CAN IMAGINED MOTOR PRACTICE CHANGE CORTICAL REPRESENTATIONS?

By

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I started doing research in high school after my grandmother was diagnosed with Alzheimer's disease. Quickly I realized that I liked the intellectual challenge and the idea that research had the potential to help people's lives. When I arrived at college, I made the decision to continue performing research and I applied for a job in two laboratories. The first laboratory conducted bench research that was similar to the type of research I had done in Miami. The second laboratory was much different. Chemicals, beakers, and rats were replaced by a large computer, brain atlases and optical discs. Immediately I was mesmerized by the fact that magnetic fields could be harnessed to provide pictures of living human brains. At that moment I decided to join Dr. Leonard's lab and it has been the best decision I have made so far in my life both from a professional and personal standpoint. That was nine years ago.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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The human brain is capable of remarkable changes in response to the environment. It is known that the cortical representations that control specific movements are adaptable and can be modulated by practice. Research in animal models and recently human subjects has shown that stimulation of the brain or repeated practice leads to expansion of cortical representations. Imagery is the process of creating vivid, mental constructs of real world actions and situations. Imagery is suggested to use the same neuronal architecture as volitional movement. The current study hypothesized that practicing a task using motor imagery would induce changes in cortical representations in a similar fashion as practice by volitional movement.

Twenty-five subjects were randomized between an executed and imagined motor practice group. Subjects in the executed group performed finger tapping of a specific sequence for fifteen minutes per day for three weeks. The imagery group also practiced finger tapping using the same sequence; however, these subjects used the

first person perspective to imagine tapping the sequence without overt movement. Functional MRI and behavioral testing were performed both before and after the practice interval to evaluate changes in neuronal activation and performance characteristics (including speed and accuracy), respectively.

Results demonstrated that both executed and imagined practice significantly improved motor performance ($f=29.09$; $p=0.001$); however, the gains with executed practice were larger ($f=7.47$; $p=0.016$). Both executed and imagined practice caused a significant increase in the size of primary motor cortex representations in the left central sulcus ($f=9.324$; $p=0.009$). The increase in cortical representations generalized and was seen during random tapping sequences; however, these subjects showed no performance improvement. The main finding demonstrated that subjects who were able to perform robust imagery obtained performance gains that were highly correlated with increases in cortical representations ($r= 0.857$; $p=0.003$).

Several theoretical neuroanatomical models are proposed to explain processes by which imagery induces cortical reorganization and performance gains. Motor imagery may be a useful adjunct to neurorehabilitation strategies since imagery is capable of causing useful improvements in performance that are based on changes in brain organization.

CHAPTER 1
INTRODUCTION

The human brain is among the most complex entities scientists have attempted to study and it has been the source of human wonderment for centuries. As early as Egyptian times humans have sought a better understanding of what makes the body and mind function. The Edwin Smith Surgical Papyrus, authored in the 17th century B.C., represents the first known written reference to the human brain [1]. In this document translated by James Breasted, the word brain is used six times to describe the symptoms, diagnosis and prognosis of two patients with head trauma. Hippocrates in the fifth century B.C. suggested that "Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant" [2]. Our struggle to understand ourselves remains as one of the most active areas of research in the medical and scientific community. Simple questions remain unanswered and our appreciation for the complexity of the human brain grows with every new discovery. Beyond the basic understanding of brain function are the more existential questions regarding how the human mind interacts with the physical milleu of the brain. Lay individuals discuss mind over matter and neuroscientists are now beginning to understand how the mind can interact and shape how the brain functions.

It has always been a desire of human beings to advance both their intellect and physical prowess. As such we have attempted all variety of strategies with the goal of either improving our mind or our body. As our understanding of the connection between the mind, the brain, and the body advances, it has become possible to test the association between mental exercise or rehearsal and the physical manifestation of these actions. The idea for mental rehearsal is not new and elite athletes and other individuals who require precise control of motor outputs, ie., neurosurgeons and fighter pilots such as the Blue Angels, have been using this technique for many years. One successful use of imagery by athletes was reported by Mahoney and Avener in 1977 [3]. They performed a retrospective study of US Olympic trial gymnasts and found those who were successful used internal imagery as a training tool. Over the last 15 years there has been much interest in the use of imagery to enhance sports performance, but little emphasis has been placed on understanding the underlying neuronal mechanisms responsible for these behavioral changes. If we could gain a better understanding of the neural foundations upon which these behavioral changes occur, then the potential to manipulate this system becomes a real possibility. The impact from this knowledge could be dramatic in the future. If we hypothesize that motor imagery reshapes motor system circuitry, then it follows that one could potentially harness the benefits of imagery to improve motor performance in disabled individuals. An example based upon this supposition would be the use of motor imagery as an adjunctive therapeutic modality for those patients undergoing physical rehabilitation following neurological injury. It is currently unknown how the improvements in performance occur following the use of imagery; however, the potential applications of

this technique to the treatment of stroke patients and others afflicted with neurological injuries are intriguing nonetheless. An understanding of the neural substrate of imagery induced change in motor function could engender more confidence in the technique and stimulate interest in the therapeutic applications.

Unlike imagery, the neural foundations underlying practiced movement are beginning to be understood. It seems possible that many of the mechanisms responsible for motor learning during executed movement will be shared by the systems subserving motor imagery. It is well known from the animal work of Nudo that motor cortex representations expand with repeated, i.e., "practiced" execution of motor movements and that the increase in the motor cortex representation is specific for the performed task [4]. Likewise, recent functional imaging studies have documented similar changes in the human brain after practiced motor movement [5]. A logical extrapolation of these findings would lead to the hypothesis that imagery may improve performance by enlarging or focusing the cortical representations responsible for programming movement. Functional imaging studies have demonstrated motor cortex activation during imagined movement; however, no studies have investigated the use of motor imagery in the context of repeated mental rehearsal [6].

The focus of this investigation was to examine the possibility that repeated imagery or mental rehearsal of specific motor sequences can expand motor cortex representations and alter behavior. This example of using the mind to enhance the physical characteristics of motor performance provides an interesting opportunity to explore the interaction between the mind and the physical substance of the brain. Does

the mind have the ability to shape the physical construct of the brain and by such action alter the physical performance of the individual?

CHAPTER 2
REVIEW OF LITERATURE

Overview

The background presented for this proposal encompasses many diverse fields and concepts. The rationale for reviewing this large variety of topics relates directly to the complex subject matter under investigation. This research paper investigates the use of imagery and its effect on cortical representations using functional MRI. As such it was important to review topics ranging from the neuroanatomy of the motor system to imagery and functional MRI. The following review addresses these topics in depth to provide a comprehensive background upon which models of brain reorganization can be based. This chapter will review the following concepts: first, the motor system will be extensively reviewed providing evidence of the neuroanatomic pathways subserving executed motor function; second, higher order motor systems will be reviewed to provide background on the cortical areas essential for the development and refinement of motor programs; third, functional imaging studies of motor movement will be reviewed to demonstrate the technique's accepted application in the investigation of motor performance; fourth, imagery will be reviewed providing current models of neural mechanisms and approaches describing how imagery can be accomplished; fifth, procedural learning will be discussed focusing on the cortical areas that participate in motor learning; sixth, mechanisms of cortical plasticity will be reviewed suggesting cellular mechanism by which learning may occur; lastly,

functional MRI will be reviewed with discussions related to the history of the technique, the physiologic process which give rise to the images, and current technical considers including task design. While the review is extensive and broad based, it serves to provide a comprehensive overview of topics directly related to the current study.

Historical Perspectives Regarding the Motor Tracts and Volitional Movement

As a prelude to reviewing the contemporary literature regarding the control of volitional movement, it is valuable to realize that this investigation is but one in a long line of inquiry into the substance and mechanisms responsible for human movement and by implication motor learning. As with most neuroanatomical investigations, the description of the anatomy preceded understanding of the function that anatomy supports. The following review is taken from Nyberg-Hansen and Rinvik (1962), and provides a brief yet informative introduction to the history of the corticospinal tract and its constituent parts [7].

Scientific discovery in centuries past was often slow and sporadic. The investigation into the pathways and structures of the motor system followed this same pattern of discovery. The first knowledge of motor system anatomy came from Willis in 1664 when he became the first to describe the pyramids of the medulla oblongata. Thereafter in 1710 Petit adequately described the decussation of the fibers based on normal anatomical and clinico-pathological human material and on experimental studies in animals. One hundred years later, Gall and Spurzheim in 1810 dissected the human pyramidal tract upwards to the cerebral cortex. They made an important contribution by suggesting the pyramidal tract received fibers from the central gyri.

Gall & Spurzheim were the first to call it a motor pathway. In 1853 Jean Cruveilhier correlated cerebral atrophy and pyramidal shrinkage with crossed paralysis, and in 1851 Turck reported that the descending fibers, after having decussated, descend in the lateral funiculus of the spinal cord as the "Pyramiden-Seitenstrangbahn." Turck further described a ventral tract, the "Hulsen-Vorderstrangbahn"; however, he was not aware of the relationship between these two tracts. Later Bouchard, in 1866, understood that the two tracts described by Turck were both parts of the pyramidal tract and he named them "faisceau encephalique croise ou externe." In 1883 Schafer described the uncrossed lateral corticospinal tract in the macaque and the following year Pitres observed the same tract in man. Pitres also described a ventral crossed corticospinal tract in some of his human pathological cases. These classical investigations into the structural foundations of the motor system have been confirmed and extended by numerous other investigators.

A more recent historical record details attempts to understand motor function. The search for localization of motor function was first proposed by Hughlings Jackson in 1864 when he noted an association between a speech defect and right sided chorea. He stated that he saw "no more diffuculty in supposing that there are certain convolutions superintending those delicate movements of the hands which are under the immediate control of the mind, than that there is one, as Broca suggests, for movements of the tongue in purely mental operations" [8]. In 1870 Gustav Fritsch and Eduard Hitzig provided the first direct evidence that control of motor movements was predominantly represented in the contralateral primary motor cortex [2]. They found that by applying a galvanic current through bipolar electodes to the anterior half of the

dog's hemisphere, they could obtain movements in muscles groups in the opposite half of the body. Later, Leyton, Grunbaum and Sherrington suggested that motor effects are elicited most readily from the contralateral precentral gyrus in primates [9, 10]. They noted that the excitable cortex is limited to the precentral gyrus and that in no case did they find primary motor response behind the fissure of Rolando. They obtained discrete movements of the ear, nostril, palate, lips, jaw, vocal cords, chest and abdominal wall, pelvic floor, anal and vaginal orifice as well as of the extremities. In 1892 Ransom was the first to stimulate the cortex of a conscious patient and produce both sensation and movement [11]. In 1938 Wilder Penfield and Edwin Boldrey published the first concise description of human motor representations studied using electrical stimulation [12]. They also introduced the concept of the human motor homunculus. Regarding the movement of the fingers, they noted that "although the responsive points extend 5 ½ cm along the length of the fissure of Rolando, very few are found more than 1 cm distant from it" (p. 411). Of the 102 recorded points, 77 were precentral and 25 postcentral with the most common movement being movement of all the fingers in unison. Interestingly, Penfield also noted that the points for one digit were sometimes found separated rather widely as though "these members had a comparatively large amount of cortex devoted to them"[12].

The brief description of the historical background of the motor system was divided between structure and function; however, it is known that these two percepts are inextricably linked. Often many of the structures that make up the physical substance of the motor system are the same structures that provide for the intricate motor program that controls volitional movement. Darian-Smith provides a brief

description of the mechanisms behind manual dexterity [13]. This description provides a compelling example of the complexity of this system. Darian-Smith suggests that manual dexterity depends on a sustained and rapid transfer of sensorimotor information between the cerebral cortex and cervical spinal cord. Effective use of the hands requires many steps including (1) a continuous input to the cerebral cortex of proprioceptive and tactile information from the spinal cord, (2) visual input for visually guided tasks, to provide a precise, dynamic representation of the external world, and the location and movement of the hand and body in that world, (3) connections that enable cross-talk between the different cortical neuron populations, not only the sensory and motor cortical fields, but also the cingulate, prefrontal, posterior parietal and temporal cortex which may be coactive during handling of an object, and 4) intact spinal circuitry in the cervical cord to affect the motor program. It is amazing that something so simple as reaching for a cup can demand so many brain resources. Darian-Smith's description seems simple; however, the component parts are each full of details which have yet to be fully understood.

Clearly the motor system is a complex system both anatomically and functionally. The purpose of the following sections is to review current understanding of both the anatomy which supports motor function and the complex interactions of different brain regions that create the motor program, i.e., the functional component of movement. First, the review will cover the current understanding of motor system neuroanatomy including describing the pyramidal tract, brain stem pathways, and ipsilateral corticospinal projections. Second, the effects of maturation and aging on motor system development will be discussed as an example of how we acquire skilled

movement. Third, the current thinking regarding the control and formation of volitional movements will be reviewed. The discussion will focus on both cortical and subcortical systems implicated in the creation and maintenance of motor programs. Finally, current functional imaging research will be reviewed that demonstrates in vivo the contribution of many of the structures discussed. The goal in the first section of this chapter is to review the primary motor system and the higher order systems responsible for the production of skilled movement as a prelude to discussing the concepts of motor imagery, motor learning and plasticity. These later concepts integrate and built upon current understanding of motor system anatomy and function and provide the basis for investigation into imagined motor practice and its effects on cortical representations.

Neuroanatomy of The Motor System

Pyramidal Tract

The pyramidal tract fibers originate from cortical and subcortical structures and descend toward the medulla by way of the cerebral peduncles. The decussation in the medulla forms the main pathway for motor output from the cerebral cortex and represents the main source of descending fibers that terminate directly on motoneurons in the ventral horn of the spinal cord, particularly those innervating distal muscles. Contemporary anatomical doctrine states that the fibers of the corticospinal tract decussate at the level of the medullary pyramids. It is estimated that approximately 75 percent of descending fibers cross to the contralateral corticospinal tract while the remaining 25 percent remain uncrossed, contributing fibers to the lateral and ventral uncrossed tracts. As the pyramidal tract contains motor projections, it has long been

accepted that a lesion of the pyramidal tract usually results in a spastic hemiplegia with impairment of skilled voluntary movement, increased deep tendon reflexes, and weakened or absent cutaneous reflexes with an extensor plantar response; however, each of these physical findings may not always be present, as limited case reports have found preservation of distal extremity function following isolated destruction of the pyramidal tract [14]. The complex nature of the physical findings that occur following lesions of the pyramidal tract and the possible preservation of some of these functions alludes to the complexity of this system and our incomplete understanding of it.

To fully understand the mechanisms responsible for volitional movement one must understand the complex anatomy of the corticospinal system. The cerebral peduncles provide a starting point and illustrate the complexity underlying the descending fiber tract's trajectories. As noted, prior to descending to the pyramidal decussation in the medulla, the fibers of the corticospinal tract pass through the cerebral peduncles. Bucy et al.(1966) reviewed the composition of the cerebral peduncle in the monkey, outlining the following descending fiber systems [15]. The medial fourth or fifth contains fibers from the frontal cortex anterior to the precentral motor area. To date, the termination of these fibers is poorly understood. Fibers from the precentral motor cortex (Brodmann's areas 4 and 6) also traverse the medial fourth and fifth of the cerebral peduncle to terminate in the pons and cerebellum. These pathways are concerned with coordination of skeletal muscular control. These fibers originating from the precentral cortex traverse the medial fourth and fifth of the cerebral peduncle synapse in the tegmentum of the brainstem and are concerned with control of motor nuclei of cranial nerves, muscular tone of visceral structures and vascular functions.

The central half of the cerebral peduncle contains corticospinal fibers from the precentral motor cortex, subdivided so that those for the upper extremity lie medially, just lateral to the corticobulbar fibers. Lateral to the fibers concerned with the arm lie the corticospinal fibers to the trunk and even further lateral lie the fibers concerned with the lower extremities. This group of fibers represents approximately 60 percent of the fibers passing down through the medullary pyramids, and these fibers control skeletal musculature through their termination on anterior horn cells. The lateral fourth segment of the cerebral peduncle is composed of fibers from the parietal cortex, being further divided into parieto-spinal and parieto-bulbar fibers. The parieto-bulbar fibers go to the nuclei gracilis and cuneatus and the sensory nuclei of the fifth cranial nerve. The parieto-spinal fibers constitute the remaining 40 percent of the pyramidal tract. Many of these cells terminate on the cells of the posterior horn of the spinal cord. The cerebral peduncle is but one segment of the complex corticospinal tract. To understand the mechanisms responsible for dexterous hand movement, it is useful to understand the cerebral cortex and the likely sites responsible for the physical initiation of volitional movement.

Dexterous movement of the digits is a fairly recent ability along the evolutionary spectrum, and many scholars agree that this capacity is linked to the great success of our species. Evolutionary evidence suggests that the corticospinal tract (CST) has evolved in primates and humans to facilitate dexterous movement with the neocortex being the primary site of evolutionary change. Nudo et al. (1995) examined the evolutionary changes in the corticospinal tract morphology, noting that the evolution of the CST in the anthropoid primate lineage was marked by increases in total

numbers of somata, increases in soma size, decreases in density, and substantial changes in the distribution of somata within the neocortex [16]. Nudo speculates that the large relative decrease in concentration and surface density of corticospinal somata may be related to an increase in local circuit neurons and in the cortical neuropil related to the corticospinal neurons. A relative decrease in projection neurons, with a concomitant increase in local circuit neurons, may allow for a more adaptable system capable of the revolutionary motor dexterity seen in human. The importance of the neocortex is that it is the origin of the efferent projections to the spinal cord and thus the site of initiation of volitional movement. Contemporary studies in humans have attempted to describe the distribution of motor cortex neurons and their subsequent projections to the spinal cord. An important distinction is whether neurons in these various regions of the neocortex terminate directly on the ventral motor horn cells. It is believed that neurons terminating directly on ventral motor horn cells directly contribute to skilled voluntary movement.

Nyberg-Hansen and Rinvik (1962) reviewed the historic and contemporary literature regarding the origin and termination of the pyramidal tract in humans [7]. A summary of the more recent findings regarding the origins of the pyramidal tract, as exemplified by the work of Russel and DeMyer (1961), found that 40 percent of descending pyramidal axons arose from the parietal lobe (Brodmann's areas 3,1,2,5 and 7), 31 percent came from area 4 and the remaining 29 percent arose from area 6 [17]. The diffuse nature of the origins of the pyramidal tract lead Mettler (1944) to conclude that a complete hemispherectomy was necessary in the monkey to produce a complete disappearance of fibers in the medullary pyramid [18]. Together these reports and

others cited by Nyberg-Hansen and Rinvik demonstrate that the pyramidal tract is comprised of fibers with multiple sites of origin. It is important to note, however, that the authors describe the precentral gyrus (Brodmann's area 4) as contributing the most fibers to the pyramidal tract with axons that directly terminate on the ventral motor horn cells. " Since the digits of both extremities are represented in the anterior wall of the central sulcus and since the Betz cells are found chiefly in this region [we] suggest that the rapidly conducting axons of the Betz cell make up many, or all, of those axons which establish monosynaptical contact with motoneurons." (p.7) [7] Prior to this paper Kuypers (1960), investigated lesions of the posterior precentral gyrus, suggesting that neurons with direct terminations on ventral horn motor neurons form the basis of "skilled voluntary movements" (p. 7) [19]. These studies corroborate the findings presented by Penfield and Boldrey (1938) that direct electrical stimulation of the posterior margin of the precentral sulcus elicited individual movement of the fingers from 23 of 77 precentral locations stimulated [12]. Clearly this work demonstrates that the precentral gyrus plays a major role in the formation of skilled movements; however, it was work performed by Lawerence and Kuypers in 1968 that provided definitive evidence that the corticospinal tract, originating from primary motor cortex, is essential for fractionalized finger movements.

Lawrence and Kuypers (1968) provided definitive evidence that the corticospinal pathways provided for speed and agility of movement and for a high degree of fractionalization of movement as exemplified by individual finger movement [20, 21]. Using monkeys with pyramidotomy lesions, they found that bilateral lesions confined to the pyramidal tract produced few behavioral problems following lesion

surgery. At one month post-operative the animals were able to pick up food by closing all the fingers in concert, had accurate reaching movements and were able to perform normal monkey activities of daily living. Importantly, the main deficit was limited to the ability to produce what was termed a "precision grip", the opposition of the index finger with the thumb. At no time in the recovery period could any of the animals remove food from a well 0.9 cm in diameter. The inability of the animals to perform this simple task resulted from their inability to use their fingers independently, in contrast to normal animals that were able to complete the task using a precision grip.

Lawrence and Kuypers noted some animals had preservation of some distal extremity movements after the lesions were performed. They subsequently noted that animals with some corticospinal fibers spared, regardless of their location, eventually had some return of individual finger movements. Lawrence and Kuypers speculated that the preservation of some descending corticospinal pathways would represent one mechanism for recovery of distal movement following a lesion. They suggest a second method of preservation of function could be due to the involvement of medial and lateral subcorticospinal pathways which they clearly implicated in the preservation of gross movement following bilateral pyramidotomy [20]. In their second classic paper discussed in the next section, Lawrence and Kuypers attempted to elucidate the role of the pyramidal tract versus the contribution brain-stem pathways have in producing distal extremity movements. The findings of this follow up paper suggested that the corticospinal pathways are not necessary for gross movement; however, they are essential for independent finger movements.

Descending Brain Stem Pathways

Besides the direct pathways utilizing the pyramidal tract, the descending brain stem pathways likely play a role in the control of some distal extremity movements, and some authors contend descending brain stem pathways are capable of controlling skilled voluntary movements. The most likely is the ability of extra-pyramidal systems to provide for independent limb movements and total body-limb activity. Nyberg-Hansen and Rinvik (1962) reviewed the variations of the pyramidal tract in man and suggested that extra-pyramidal systems may be capable of controlling skilled movements. They noted that 'the pyramidal tract is not the only cortico-fugal pathway which may be engaged in the performance of skilled voluntary motor movements . . . the cortico-rubro-spinal pathway may be of importance for this function" [7]. A case report by Bucy and Keplinger (1961) corroborates this view, documenting a surgical procedure for Parkinsonian tremor that divided the lateral 11mm of the cerebral peduncle to a depth of 6 mm. The procedure left the patient with "very mild weakness in the extremities" and with "remarkable control [of the fingers and toes], although not quite perfect"[22]. As discussed, Lawrence and Kuypers (1968) investigated the role of the "extrapyramidal" pathways after pyramidectomy and described the anatomy of the descending brain stem pathways [21]. Their research supports the most widely held view that the descending brain stem pathways likely provide for independent limb movements and total body activity but likely play little role in controlling skilled movements. A brief review of the descending brain stem pathway anatomy is presented followed by a discussion of Lawrence and Kuyper's work in this area.

In the monkey the subcortical pathways which descend throughout the spinal cord have been grouped into a ventromedial and a lateral system based on the terminal distribution pattern in the spinal grey matter. Fibers of the ventromedial system occupy the ventral and medial position in the lower brain stem and descend in the spinal cord in the ventral, the ventrolateral and the medial parts of the lateral funiculi. The fibers of the ventromedial system are derived from the vestibular nuclei, the interstitial nucleus of Cajal, and the medial pontine and medullary reticular formation. These fibers terminate preferentially in the ventral and medial parts of the internuncial zone. The fibers of the lateral system occupy a lateral position in the lower brainstem and descend into the lateral funiculus of the spinal cord. The fibers of the lateral system are derived from the pars magnocellularis of the red nucleus. These fibers terminate preferentially in the dorsal and lateral parts of the internuncial zone.

Lawrence and Kuypers extended their initial study [20] providing evidence for the role of descending brain-stem pathways in post-pyramidotomy recovery [21]. It is suggested that normally precentral cortex is able to influence the brain-stem pathways; however, following bilateral pyramidotomy this inhibition is removed. Lawrence and Kuypers found lateral-brain stem pathways facilitate distal extremity movements, hand movements and the ability to flex an extended limb. Lesions to the ventro-medial brain stem pathway resulted in flexion bias of the trunk and limbs and severe impairments of axial and proximal movements; however, distal extremity movements were unaffected. The overall conclusions reached by Lawrence and Kuypers reflect the capacity of brain-stem pathways to substitute control for pyramidal pathways. They speculate that after destruction of precentral projections, the interneurons readjust to become more

responsive to lateral brain-stem pathway excitation. The alternate pathway using the lateral brain-stem system can then facilitate distal movements. It is important to recall, however, that fine precision grip was still impaired in these animals, suggesting the critical importance of direct cortico-pyramidal-spinal projections for this movement component. It seems clear that the control of skilled distal extremity movements requires an intact pyramidal pathway; however, the potential for other pathways, such as the descending brain stem or ipsilateral pyramidal pathways, to contribute some element of control for these skilled movements has not been completely resolved..

The recovery of function noted in these animal studies could be accounted for by lateral brain-stem upregulation and/or by preservation of some descending pyramidal tract pathways; however, it is also important to consider the contribution of the uncrossed ipsilateral corticospinal tract when evaluating post-lesion or stroke recovery. The age at which the lesion occurs is another factor involved in the extent of recovery. Children who suffer large perinatal strokes that would kill most adults survive, recover, and live productive lives. Both of these subjects are important ideas that expand our understanding of how complex the human motor system is both structurally and developmentally. Both of these subjects will be reviewed in turn beginning with the contribution of ipsilateral corticospinal projections and their role in motor control.

Ipsilateral Corticospinal Projections

Pyramidal pathways also have a fairly large component of ipsilateral cortical projections. These fibers may also play a role in the control of distal extremity movement. Although most corticospinal fibers decussate in the medulla to form the

contralateral corticospinal tract, 25% remain uncrossed [7, 23]. Of these, 15% continue as the ventral corticospinal tract, which mainly decussates in the spinal cord to innervate the contralateral side. The remaining uncrossed fibers stay in the ipsilateral lateral corticospinal tract and contribute to arm movement. Glees and Cole (1952) suggested that "uncrossed tracts" may be available to a patient in an "emergency" [24]. Glees and Cole presented a histologic case where there was complete pyramidal degeneration of the right medulla, while the other side was left intact. Apart from the crossed degeneration at the spinal cord levels on the left side, a well marked ipsilateral degeneration was found in the right lateral corticospinal tract. Brinkman and Kuypers (1973) addressed the contribution of ipsilateral motor projections in experiments performed on split-brain monkeys [25]. Based on Kuyper's earlier work [20, 21, 26], it was suggested that one half of the brain was connected to both the ventromedial and dorsolateral parts of the intermediate zone and to motoneurons of distal extremity muscles on the contralateral side; however, projections also reached the ventromedial parts of the intermediate zone ipsilaterally. This research implies that each half of the brain has full control over arm, hand, and finger movements contralaterally, but only some arm movements ipsilaterally. Results from Brinkman and Kuyper's paper [25]suggested that individual movements of the hand after contralateral lesions were the result of lateral brain-stem pathways that originated from the magnocellular portion of the red nucleus ipsilaterally. The red nucleus receives projections exclusively from the ipsilateral precentral gyrus and these projections remain ipsilateral as they access the ipsilateral corticospinal tract. Even after destruction of the ipsilateral fronto-parietal neocortex, some independent hand movements were noted even though this tract was

understood to be the only ipsilateral projection to the ipsilateral corticospinal tract. An interesting secondary finding was the speculation that visual systems were able to access the lateral brain-stem pathways to facilitate movement even after destruction of the ipsilateral fronto-parietal neocortex . Clearly the ability of the brain to adapt to injury and carry on basic functions critical to the organism's survival are most robust.

Nathan and Smith (1973) addressed the possible contribution of ipsilateral projections and crossing fibers in their report on the effects of two unilateral cordotomies on the motility of the lower limbs in patients with intractable cancer pain [27]. The authors noted that the first unilateral lesion caused paresis of the ipsilateral lower limb that in time regressed with recovery of limb function. The second cordotomy on the contralateral side resulted in immediate loss of all recovered function. It was suggested that recovery had been produced by descending fibers of either or both lateral corticospinal tracts. Possible pathways suggested included the ipsilateral lateral corticospinal tract, the contralateral lateral reticulospinal tract and the contralateral "tegmento-rubra-spinal" tract. The authors note that Sherrington looked at the lateral corticospinal tract as the typical example of a "recrossed tract" later noting that Liu and Chambers (1964) found that some of the fibers of both the ventral and lateral corticospinal tracts cross the cord in the dorsal grey and ventral commissures in the macaque[28]. Gazzaniga et al. (1967), looking at dyspraxia following division of the cerebral commissures, found that with pure lesions of the commissures, in which each hemisphere was preserved in good functional condition, the capacity of the two hemispheres to direct ipsilateral as well as contralateral movement makes for a "minimum of praxic disturbance" [29]. In Gazzaniga's study, it was noted that

ipsilateral control appeared to be strongest for movement of axial structures in the head, neck, and trunk, and weakest over the thumb and fingers, especially of the right hand in right-handed subjects.

Recent research has tried to address the question of how ipsilateral motor cortex controls distal hand movement. Tanji et al. (1988) studied single cell activity in monkey motor cortex and its relation to motor activity, concluding that 8.2% of all movement related neurons were ipsilateral to the side of motor performance [30]. Tanji et al. suggest that ipsilateral cortical connections play a minor role in simple movements, but may become more potent when they are called into action following circumstances such as a stroke. Similarly, Salmelin et al. (1995) using MEG, demonstrated enhanced activation of the ipsilateral primary motor cortex both prior to and during increasingly complex unilateral finger movements [31]. Salmelin noted that voluntary movement was associated with changes in neuronal activity starting about one second before movement onset and lasting for two or three seconds after return to the resting condition. The ipsilateral motor evoked field (MEF) was actually dominant during complex tasks that involved multiple digits. This finding suggests the importance of the ipsilateral somatomotor cortex in complex motor tasks involving multiple digits. It was also noted that the contralateral MEF always preceded the ipsilateral MEFs, but the interval was drastically reduced for rapid digit sequences. Salmelin concluded that ipsilateral somatomotor cortex is active both during preparation and execution of unilateral hand movement and that the intensity of activation is strongly dependent on task difficulty.

As discussed by Salmelin, the role of ipsilateral corticospinal pathways in normal movement may be to facilitate coordination of complex movements. The recruitment of ipsilateral corticospinal neurons may promote coordination of fractionated movements. A finding that supports this idea was reported by Jones and colleagues (1989). In stroke patients, distal extremity movements are impaired compared to normal controls on the ipsilesional side, even though the contralateral corticospinal projections are intact [32]. Wassermann and colleagues (1991) further investigated this finding. Transcranial magnetic stimulation (TMS) mapping was used to activate motor cortex in normal subjects. The authors reported that there was an inhibitory pathway from the motor cortex to the distal and proximal muscles of the ipsilateral upper extremity that act by decreasing the excitatory input to spinal motoneurons [33]. Wassermann et al. suggest that the loss of inhibitory input may account for the deficits in fine motor control described in the extremity ipsilateral to a hemispheric lesion. Hemispheric dominance was also investigated to determine if ipsilateral control is more pronounced from the dominant hemisphere. Singh et al. (1998), using functional MRI, reported that in right-handed subjects, ipsilateral activation was significantly greater during non-dominant (left) hand tasks while, in left handed subjects, activation was similar for each hand [34]. It was noted that ipsilateral activation was most pronounced in the precentral/premotor cortex. Singh et al. concluded that hemispheric dominance for movement may play a role in the different patterns of ipsilateral activation. In addition to questions regarding hemispheric dominance, the type of movement that activates the ipsilateral pathways may be distinct. Kawashima et al. (1994) investigated the role of ipsilateral primary motor

cortex during two types of motor tasks performed with the ipsilateral hand [35]. One task involved "length discrimination" and the second task involved a tactile discrimination. The results of this study found activation in the ipsilateral primary motor cortex during the length discrimination task but not during the shape discrimination task. Kawashima et al. suggest that the primary motor cortex role may be more complex than just controlling contralateral motor function. Ipsilateral primary motor cortex may constitute part of a neural network which must be engaged in the performance of a task such as length discrimination.

At this point, research findings suggest that ipsilateral corticospinal projections play a role in the control of skilled movement; however, the exact nature of their influence is not well appreciated. Ipsilateral projections likely play a role in the coordination of skilled movement in healthy subjects, possibly more so for the non-dominant hand. The potential influence of the ipsilateral pathways is most robust in patients who have suffered a motor stroke and recent functional imaging studies are beginning to support this idea. The role of the ipsilateral pathways could be one of subordinate collaborator since contralateral pathways that have developed through evolution as the dominant effector of the motor program.

Ipsilateral and Contralateral Corticospinal Pathway Dominance

Ipsilateral primary motor cortex and brainstem pathways are probably relegated to a subordinate role during normal motor system performance and development. A hierarchy of dominance is likely exerted in the motor system principally by the hemisphere contralateral to the desired movement with this dominance strengthening as the individual matures and develops motor skill. The dominant motor cortex

(contralateral to the movement) likely controls or regulates the output from ipsilateral corticospinal neurons and in a similar fashion regulates brain-stem pathways through upper motoneuron signaling at the level of the spinal cord. This has broad implications for stroke recovery, as disinhibited cortical neurons may facilitate recovery by acting independently to produce movement. The lateral brain-stem pathway terminates in the dorsal and lateral parts of the internuncial zone; however, direct corticospinal projections also make terminal connections in the lateral zone and can exert influence over the brain-stem pathway [21]. Likewise, ipsilateral projections normally play a subordinate role in control of motor output responses. Muller et al. (1997) studied the ontogeny of ipsilateral corticospinal projections using transcranial magnetic stimulation (TMS), finding that ipsilateral motor evoked potentials were absent after age ten and postulated that this disappearance of ipsilateral corticospinal activity was due to an increase in transcallosal inhibitory signaling [36]. Muller et al. postulated that ipsilateral intrahemispheric inhibitory mechanism may also play a role in suppressing ipsilateral corticospinal neurons. The release of inhibition following a stroke could promote recovery. Muller et al. speculated that cortical motor neurons become "unmasked" after a hemispheric lesion due to the lack of tonic transcallosal inhibitory influence. Supporting this hypothesis, Caramia et al. (1998) using TMS found ipsilateral activation in patients with frontoparietal cerebral gliomas [37]. Caramia et al. noted ipsilateral motor evoked potentials in patients but not in normal adult subjects. Caramia also speculated that ipsilateral motor control may be possible and it likely plays a compensatory role when contralateral routes are damaged. Cao et al. (1998) investigated the functional MRI activation patterns seen after poststroke hemiparesis

[38]. Results demonstrated ipsilateral sensorimotor cortex activation during paretic hand movements in six of eight patients studied. Normal right handed subjects rarely show ipsilateral activation during simple finger tapping with the dominant hand. Cao et al. conclude that preexisting uncrossed neural pathways may be accessed and recruited to compensate for damage to the crossed motor pathways after ischemic stroke. Functional motor pathways may reorganize in an attempt to recruit any prestroke link between the paretic hand and the primary motor cortex in the noninfarcted hemisphere via uncrossed corticospinal tracts or other indirect uncrossed pathways.

As discussed, the ipsilateral pathways may play a role in the recovery from stroke due to their ability to control distal movements, at least in a limited fashion. While it seems plausible that ipsilateral projections can collaborate in the control of fine skilled movements in healthy subjects, more research is needed. If this hypothesis is supported, then it would have implications regarding how we think the motor program is developed and executed. By extension this would then impact on our understanding of motor learning and imagery, especially if we believe these tasks share common neural pathways and mechanisms. Since studies of normal subjects have shown ipsilateral activation on finger tapping tasks, we believe our research may provide further findings regarding this interesting topic. Complex finger tapping sequences, as provided for in the current study, may promote the activation of ipsilateral pathways.

Effects of Maturation and Aging

The effects of maturation and aging have a direct impact on the ability to perform skilled movements. Likewise, the structural integrity of the motor system likely has a direct influence on the development of the motor programs and their

subsequent execution. Imagery may use the same neuronal mechanisms as executed movement and any developmental or age-related abnormalities would negatively impact on motor imagery or the performance gains it might render. These variables would impact any translational research that might develop from studies of imagined movement and its application to neurorehabilitation, as an example. All indications suggest that proper motor system development is critical for rapid, skilled movement. Maturation of the motor system may occur on two different but related fronts, structural and functional. Structural changes occur in processes such as myelination of tracts while functional changes occur in cortical organization and refinement of the motor programs which specify exact movement sequences. Looking at the fibers of the pyramidal tract from an ontogenetic viewpoint, Lassek (1942) concluded that all axons are present at birth [39]. He found that at the age of eight months, when voluntary movements are attempted, some fibers commence to increase in diameter more rapidly than others. At the age of 22, the pyramidal tract possesses many small axons, some medium sized and a few large axons. The overall cross sectional area is reported at 11.7 sq. mm. During development it may be that the contralateral fibers are preferentially myelinated as motor skills develop and cortical inhibition is exerted on ipsilateral projections. Olivier et al. (1997) also looked at the change in electrophysiologic properties of the postnatal corticospinal system in the Macaque monkey [40]. Using TMS, Olivier et al. provided data that were consistent with the idea that fine finger movements are not observed before functional corticomotor neuron connections are well established and that rapid changes in the physiological properties of the corticospinal system coincide with the period in which precision grip is known to

mature (3-6 months). Olivier further speculates that corticospinal development continues long after simple measures of dexterity indicate functional maturity, and that these changes may contribute to the improved speed and coordination of skilled hand tasks. The importance of development and developmental milestones cannot be overvalued, as all motor functions ultimately rely on the foundation created during the early years of maturation. Functions such as motor learning and possibly motor imagery may interact at the level of the spinal cord causing either volitional movement and/or making local connections to ascending sensory fibers. A properly developed corticospinal tract may be essential for these cognitive efforts to effectively alter and shape the motor program.

While the maturation of the corticomotor system is important it is but one factor in the development of skilled hand movement. In addition to the direct descending connections to the spinal cord, the extensive changes that are occurring at the cellular level of motor cortex must be considered. Along these lines, synaptic density has been shown to correlate with the development of complex locomotor skills in the rat [41]. Markus and Petit found that the peak in synaptic density occurred around post-natal day 30 and that this peak was followed by an initial sharp decline, and then by a gradual decline or plateau into adulthood. The initial sharp decline in synaptic density supports a model referred to as selective stabilization. The selective stabilization model suggests that during development many extra synapses are initially formed, some of which are later eliminated according to their usage.

The refinement in connectivity is likely reflected in the adult subject's ability to perform precise skilled motor movements. As discussed earlier, skilled movement is

influenced by a variety of factors, one of which is contralateral dominance of hand motor control. Mirror movements represent a clinical example of a defect in motor system development. In children and adults with persistent mirror movements, it is thought that the central nervous system is immature [42]. Mirror movements interfere with the performance of precise hand skills, particularly those requiring intermanual coordination. Mirror movements are common in normal children but, importantly, they are known to decrease in intensity and occurrence as children mature [43]. Persistent mirror movements are thought to reflect activity in the uncrossed ipsilateral corticospinal projection from the cortex controlling the voluntary hand movement [44]. However, it has also been suggested that mirror movements are produced by bilateral cortical activity, possibly as the result of the lack of callosal inhibition [45]. Mayston et al. (1999) studied the electromyographic activity in adult and children subjects as they performed sequential finger-thumb opposition or repetitive finger abduction [42]. They concluded that during a simple unilateral movement, the activity of the cortex ipsilateral to the active hand is suppressed with increasing age. The suppression is likely related to interhemispheric inhibition that becomes more powerful as myelination of the callosal fibers develops. Mayston et al. also note that the development of a more precise motor program that occurs as the result of practice could contribute to a more lateralized pattern of neural control producing the more skillful activity that emerges during development. It may be that a combination of synaptic pruning and maturation in response to the initial use and later refinement of motor programs leads to a concomitant myelination of descending pathways. The order and rate of myelination may be influenced by the strength of cortical connections, thus favoring contralateral

projects as evidenced in the adult. To contrast these concepts posited by Mayston, it is interesting to study what occurs as motor functions decline with age.

Age-related changes in motor performance and cognition are common even in healthy older subjects [46]. This suggests that subtle degenerative changes may occur in brain regions during the normal process of aging. The physical results of aging include decreased strength, trainability, and reduced force control. These changes are commonly expressed as abnormalities of posture, stride and coordination. Roos et al. (1997) suggest that motor unit firing rates may be affected by age-related limitations in the excitability of the corticospinal tract, the motor neurons or a reduced central drive [47]. Tobimatsu et al. (1998) investigated the effects of age on motor evoked potentials using MEG, finding that age had a significant effect on the motor evoked potentials in both the leg and hand [48]. It is suggested that these physiological changes may be related to the age-dependent changes seen in Betz cells in older subject. These types of physiologic changes are reflected in the gross appearance of the corticospinal tract. As discussed, at the age of 22 the pyramidal tract possesses many small axons, some medium sized axons and a few large axons. The overall cross-sectional area is reported at 11.7 sq. mm. while at age 80 it has diminished to 7.3 sq. mm., only 62 percent of that of an individual at age 22. This finding corroborates that of Scheibel, who reported a loss of approximately 75 percent of Betz cells by the seventh decade of life [46]. However, a more recent study by Tigges et al. (1989) found a steady decrease in the number of neurons in area 4 of the maturing monkey but no significant change in the number of Betz cells [49]. If changes with aging are not related directly to the number of Betz cells, it may be that the age-associated changes in motor performance are

related to synaptic changes in the precentral cortex. In this regard, Adams (1987) compared the synaptic changes in the precentral cortex of aging humans [50]. Results indicated that in the precentral gyrus there was a significant decrease in the number of synapses. In a separate publication [51], Adams reported that there was an accompanying increase in synaptic length in the postsynaptic contact zone in these individual brains. She suggests that the motor cortex is capable of synaptic plasticity in response to aging induced synaptic loss and that the increase in postsynaptic length may reflect an attempt by the remaining synapses to compensate for the synapses that are lost. It is not known whether these changes in the motor cortex reflect a primary loss of neurons or are the result of the loss of afferent projections from subcortical structures impacted by the aging process. Two subcortical brain regions where age-related changes have been reported include the nucleus basalis of Meynert and the locus coeruleus [52, 53]. These nuclei have extensive afferent projections, cholinergic and noradrenergic, respectively, to the cortex. Neuron loss as well as a decline in both neurotransmitter systems have been implicated in aging humans [54]. It is clear from these studies that multiple changes are occurring on the cellular and gross level during development and aging. These changes must impact upon the expression of the neural motor programs initially in a beneficial manner during development and later in a detrimental manner as we age. The concepts of maturation and aging of the motor system can impact on the ability to translate motor and imagined movement paradigms to young or older populations. Research into imagined practice may translate into future therapeutic applications in the field of neurorehabilitation, thus an understanding of the mechanisms of motor development and aging are relevant to our discussion.

Pyramidal Tract Summary

The prior discussion focused on the connectivity, development and aging of the pyramidal system. The neurons and tracts that make up this system represent the basic pathways through which complex motor programs are expressed as physical motion. It is likely that the crossed pyramidal tract is the main player in skilled volitional movement of the hands; however, the contribution of brainstem and ipsilateral pathways are just beginning to be appreciated and we may find their role to be significant and integral for efficient, highly fractionated movements of the hand. While the efferent motor system is highly complex, it may be reasonable to consider the pyramidal tract and the other associated pathways as a lower order motor subsystem that acts as the effector of motor programs developed by higher order motor systems. As will be discussed in the next section, it is likely that the production of simple or complex motor programs result from the cooperative association of many neocortical and subcortical regions. The design and implementation of motor programs by higher order motor subsystems likely represents the first step in the production of even simple motor tasks such as finger to thumb opposition and is undoubtedly critical for motor imagery and learning.

H!gher-Order Motor Subsystems

Selecting and retrieving the proper movement is as important as the production of movement itself. Without proper movement selection movements will not be goal directed and purposeful. Higher order motor systems constrain the primary motor cortex and facilitate movements that are appropriate for the task at hand. Higher order processing is highly complex requiring the integration of a host of variables.

Variables range from issues of how and when to initiate movement to issues as complex as the sequencing of individual component movements during complex tasks. Beyond the sequencing of events and the motor components called into action, attentional mechanisms become critical for proper movement. Movements are usually made either in reaction to environmental changes, or to accomplish some goal-directed task in personal space. To coordinate production of accurate movement programs, abstract concepts such as personal and extra-personal space must be integrated. An internal coordinate system to mark where our limbs are in space must also be maintained. Beyond actually moving, preparing to move involves other mechanisms that either allow us to react to our environment or initiate movement solely by internal will. The integration of these seemingly unrelated issues is critical if actions are to be performed in a logical and purposeful fashion. As will be discussed, a host of human neurological diseases disrupt this fragile intercoordinated system to produce movement disorders. Other disorders of attention and intention impact upon movement initiation and overall motor performance. The following discussion will show that the higher order motor systems are the driving force behind complex movements, feeding the sequenced and highly refined movement program to the primary motor cortex for efferent distribution to the musculoskeletal system. After the conclusion of this section, the properties and mechanism of motor learning and motor imagery will be discussed. Current research supports the idea that many of the higher order motor systems are highly conserved, being used for motor learning and motor imagery as well as for the production of the motor programs that make skilled movements possible.

Cortical Higher-Order Motor Areas: Medial and Lateral Premotor Cortex and the Parietal Lobe

We begin by addressing one of the principal cortical regions involved in the programming of motor routines; the supplementary motor area (SMA). Early studies suggested that the SMA was preferentially involved in the generation of internally driven movements rather than sensory guided movements; however, more recent investigations have suggested a more extensive role for the SMA. Goldberg (1995) suggests the SMA plays an important role in the development of the intention to act and the specification and elaboration of action through its mediation between medial limbic cortex and primary motor cortex [55]. To understand the current thinking regarding the role of the SMA, we must understand the anatomy of the system both from a structural and functional standpoint.

The supplementary motor area, also referred to as the medial premotor cortex, receives its cortical afferents mainly from the contralateral supplementary motor area, from other parts of area 6, from the somatosensory areas 3,1,2 and 5, and from the primary motor cortex [56]. Imaging studies of cortical and subcortical regions have expanded understanding of the connectivity and cooperation among these various brain regions and have further defined the role of the SMA in the execution of movement. Roland et al. (1980) studied the organization of voluntary movements and the role of the SMA in humans using regional cerebral blood flow studies [57]. His results noted that the primary motor cortex controlled simple ballistic movements by itself without the input of other cortical areas. However, once the paradigm was changed from a simple to more complex task, such as different isolated finger movements, the brain required programming in the supplementary motor area to complete the task.

Interestingly, during the complex task the SMA was seen to activate bilaterally with equivalent increases in rCBF. This finding was replicated by Shibasaki et al. (1993) again using rCBF methodology [58]. Roland et al. note that the supplementary motor area and the primary motor area are both activated during the execution of learned, sequential ballistic movements of individual fingers; whereas the primary motor area alone can control repetitive flexions of the same finger. Importantly, Roland concludes that the primary motor area does not participate in the programming of motor sequences, but in their execution. It is the SMA that is integral to the creation and/or execution of the motor program for complex tasks. Roland noted that the supplementary motor area is active when a sequence of simple ballistic movements are planned and that consequently, the supplementary motor area participates in the assembly of the central motor programs. Kertzman et al. (1997), using PET to study visually guided reaching movements, corroborate this hypothesis, suggesting that premotor areas have representations of field coordinates used in updating motor plans [59]. The integration of spatial information along with the formulation of movement sequences would be critical for proper movement sequencing. Beyond the steps necessary to program the motor responses, the esoteric concept of how one initiates a motor response has lead to investigations looking at the role of both the medial and lateral premotor cortex.

Investigations attempting to subdivide the premotor area and determine its role in motor initiation began fairly recently. Goldberg (1985) was among the first investigators to separate the premotor cortex into medial and lateral components [55]. Goldberg speculates that medial components evolve from the hippocampus and use the

cingulate cortex as the limbic-cortical root. The SMA is used as the premotor center and dependence is placed on the basal ganglia for subcortical input. Medial premotor context sensitivity is geared toward internal stimuli and this area provides for fluent execution of skilled movements. The medial premotor cortex (MPC) and the lateral premotor cortex play a role in the selection of movement but the two areas differ in their specialization. Medial premotor cortex is more specialized in making the selection of movements when no cues are present [60]. Monkeys with MPC lesions are severely impaired at performing self-paced arm movements, and at relearning motor sequences, but perform well on tasks that are directed by external cues. PET studies demonstrate that subjects performing a well-rehearsed sequence from memory activate MPC. Single cell recordings demonstrate active cells in MPC during repetitive, self-paced movements and tasks performed from memory.

More recently, Picard and Strick (1996) reviewed additional evidence that the medial premotor area was subdivided into two distinct areas, namely the pre-SMA an area largely rostral to the genu in area 6aβ and the SMA proper, an area largely caudal to the level of the genu of the arcuate sulcus in area 6aα [61]. Picard and Strick note that the SMA proper has direct projections to the primary motor cortex and spinal cord; however, the pre-SMA does not have projections to either region. The input to these two regions is also different with the SMA proper receiving projections from the Vlo region of the thalamus and the pre-SMA receiving projections from the VApc region. Based on the subcortical input to these thalamic regions, it has been suggested that different portions of the basal ganglia and cerebellum innervate each cortical region. It is also interesting to note that unlike SMA proper, pre-SMA often fails to evoke

movement when intracortical stimulation is applied. Based on these findings and the associated anatomy, it has been suggested by Picard and Strick that pre-SMA function may be more closely related to the selection and preparation for movement, whereas the SMA proper may be more involved in movement execution [61]. The exact structural and functional relationship with the medial premotor area is an area of current work and debate; however, the function of the lateral premotor area seems less controversial.

Goldberg (1985) defines lateral premotor cortex (LPC) as evolving from the piriform cortex; it uses the insular cortex as the limbic-cortical root. The arcuate premotor area (infraacrcuate area 6) is used as the premotor center and dependence is placed on the cerebellum for subcortical input. Lateral premotor context sensitivity is geared toward external stimuli and this area provides for slow segmented execution of skilled movements that are input dependent [55]. The lateral premotor cortex is concerned with selection of manipulative movements. PET studies by Deiber (1991) demonstrated that lateral premotor cortex activates during tasks where subjects must select between movements rather than simply repeat the same movement [62]. LPC lesions in monkeys and patients impair the learning and relearning of conditional tasks on which the subject must learn to select between movements on the basis of external cues. Additionally, there are many cells in the lateral premotor area that increase their activity when a monkey is preparing to move, and this increase is selective depending on the movement to be made [63].

Several lines of evidence from the human lesion literature support the role of the supplementary motor cortex in the selection of movements. Strokes involving area 6 combined with the anterior cingulate (area 24,32) produce a syndrome known as

akinetic mutism. In this syndrome patients make no effort to communicate and most importantly, movements are limited to tracking targets with the eyes and body/arm movements connected with basic body functions only. Patients with unilateral lesions often recover within a few weeks [64]. A more common syndrome related to premotor cortex dysfunction is ideomotor apraxia. Ideomotor apraxia is a disorder of skilled movement not caused by weakness, akinesia, deafferentation, abnormal tone or posture, movement disorders, intellectual deterioration, poor comprehension, or uncooperativeness [65]. Patients with lesions in this area perform poorly to command, are unable to comprehend gestures, and are unable to discriminate poorly performed acts from well-performed acts. The representational hypothesis posited by Heilman and Gonzalez Rothi (1993) state that the nervous system stores motor knowledge of skilled behavior and retrieves that information from storage and implements it rather than constructing it de novo to perform a task [65]. Heilman and Gonzalez Rothi speculate that movement formulas are stored in the dominant parietal cortex in the supramarginal or angular gyrus as representations he refers to as "praxicons." Lesions that are anterior to the parietal cortex disconnect the praxicons from the premotor and motor circuits necessary for implementing skilled movements. Likewise, lesions that destroy the left premotor cortex also cause ideomotor apraxia, because the cell bodies of neurons that cross the corpus callosum to the contralateral supplementary motor cortex are destroyed.

Classic stimulation studies performed by Penfield demonstrated that stimulation of supplementary motor cortex induced complex movements of the fingers, arm and hands [12]. Whether the SMA causes these movements by enacting motor programs

created elsewhere or causes movement de novo is unclear. Anatomic studies show that supplementary motor cortex receives projections from parietal neurons where "praxicons" are stored. It then projects to primary motor cortex; however, direct connections to the spinal cord also exist. Heilman and Gonzalez Rothi (1993) believe that supplementary motor cortex is the site of the transcoding of praxic representations into motor programs or innervatory patterns that activate motor cortex [65]. Whether the supplementary motor cortex is independently capable of encoding simple motor movements is unknown; however, Biber et al. (1978) demonstrated that some supplementary motor cortex fibers project directly to the spinal cord [66]. Alexander et al. suggest these fibers terminate in portions of the ventral horn in lower cervical segments of the spinal cord [67]. The direct projection to motor neurons innervating distal hand muscles raises the possibility of monosynaptic inputs to spinal motoneurons from the supplementary motor area, analogous to those arising in primary motor cortex. Neurons in the supplementary motor cortex are somatotopically organized and in single cell studies with primates they have been shown to discharge in relation to limb movements [68] and during preparation for such movements [69].

Whether the dominant hemisphere parietal cortex is the sole repository of praxical information is not known. Further studies of stroke patients will be able to elucidate the role of parietal cortex and SMA in non-dominant cortex and its role in stroke recovery. The potential for dis-inhibition exists where the non-dominant cortex becomes active following the lost of contralateral inhibitory input. This postulate was addressed by Heilman (1993), who noted the discrepancy between the incidence of aphasia and apraxia in right-handers, suggesting praxical information normally

localized to the left hemisphere may also be located in the non-dominant right hemisphere [65].

Cerebral blood flow studies have demonstrated that SMA activates bilaterally during complex movements in normal subjects. The patterns of activation may change, however, in subjects who have had a focal stroke. These changes can occur in the form of relocated activation or increases in activation. A recent fMRI study by Cao et al. (1998) demonstrated left supramarginal gyrus and left premotor activation during left paretic hand movements in a right handed patient with a left frontal stroke [70]. Based on these findings, it may be possible to impair primary motor cortex on the left but keep the system for distributing praxical information intact. As a different example, Weiller et al. (1992) reported increased activation during PET studies of inferior parietal, prefrontal and anterior cingulate cortex, and speculated that these changes represent a potential for plastic change within the cerebral cortex itself after injury and raise the possibility that higher-order areas of sensorimotor cortex have a greater capacity for reorganization than do primary areas [71]. If Weiller's speculation about the putative ability of higher order systems to under go plasticity more readily than other cortical areas is true, this would have significance for our study, directing our attention toward the role of the SMA in motor learning.

Other cortical areas besides the supplementary motor cortex play a critical role in the production and timing of volitional movement. The parietal cortex plays many secondary roles in the production of coordinated motor output and this region is likely involved in motor imagery and learning as well. Attention and arousal, two functions mediated by parietal cortex, are critical factors needed to produce movements at the

appropriate time and in an appropriate response to stimuli. Parietal cortex, specifically the inferior parietal lobule on the right is implicated in attention and arousal through its association with the clinical syndrome known as neglect. Right sided temporoparietal lesions involving angular (Brodmann's area 39) and supramarginal gyrus (Brodmann's area 40) correlate with neglect and anosognosia. Neglect is described as a condition whereby the patient fails to attend to stimuli in the contralateral hemispace. Heilman (1993) attributes neglect to an impairment of the attentional mechanisms necessary for normal perception. The critical areas for attention include the temporoparietal-occipital junction, limbic areas such as the cingulate gyrus, subcortical structures such as the thalamus, and mesencephalic reticular formation. It was proposed that neglect is an attentional-arousal disorder induced by dysfunction in a cortico limbic reticular formation network. Simon et al. (1995) posits that two discrete syndromes of motor neglect exist and are differentiated by performance on motor tasks enacted within or toward the contra lesional hemispace [72]. Simon et al. suggest that there are two separate attentional subsystems, a parietal-lateral premotor circuit that processes information encoded in spatial coordinates referenced to the extrapersonal space and a basal ganglionic-mesial premotor circuit that processes information encoded in egocentric skeletomotor coordinates [72]. Clearly, the ability to direct attention toward a particular stimuli, either within egocentric space or in the external environment, is a critical step in formulating an appropriate motoric response or interaction. Perenin and Vighetto(1988) noted that unilateral damage to the posterior parietal cortex (PPC) of humans yields two patterns of impaired reaching for objects under visual guidance [73]. These patterns include inaccurate reaching with either hand into the visual hemifield

contralateral to the lesion, the "visual field effect," and inaccurate reaching with the hand contralateral to the lesion in either visual field, the "hand effect" [73]. Kertzman et al. (1997) also addressed the role of the posterior parietal cortex in visually guided reaching movement [59]. It was noted that extrastriate regions had increased rCBF and may provide the visual information necessary to reach out and accurately touch an object. These extrastriate regions project to the PPC as well as receive proprioceptive information from S1 and visual information from the pulvinar. Kertzman et al. conclude that it is within the PPC that the integration of visual and somatomotor coordinates most probably occurs.

The cortical areas discussed, namely the medial premotor and parietal cortex, are integral to the formation and execution of the motor program. The ability to focus attention on a task and subsequently produce a goal directed movement is a feature that is common to both volitional movement and any other task that calls upon the motor system; motor imagery is a primary example. Motor imagery, as will be discussed in later sections of this review, is thought to utilize the same neuronal mechanisms as executed movement. In fact, the role of the parietal cortex may take on a heightened significance in motor imagery, as this type of task requires a tremendous amount of attention for successful execution. Likewise, the supplementary motor area may be accessed during imagery in the same fashion as during volitional, executed movement. TMS evidence suggests that motor imagery engages the SMA and the primary motor cortex but that somewhere before the efferent copy is transformed into movement, inhibition of the motor program occurs. The concept of conservation of brain resources will be discussed, and within this context it will be reiterated that it is likely that both

the medial premotor and parietal cortex are utilized for motor imagery as well as for executed movements.

Subcortical Motor Control and Feedback Loops

The cerebral cortex plays many roles in the formation and execution of motor tasks. The primary motor cortex, along with the corticospinal tract, acts as the primary effector of motor programs developed by the premotor and parietal cortex. In addition to these hemispheric regions, subcortical areas play a major role in movement control through the utilization of complex feedback loops.

The term basal ganglia refers to the major telecephalic subcortical nuclei that lie at the base of the forebrain. These nuclei include the caudate nucleus, the putamen, the globus pallidus, the amygdaloid complex, and the claustrum [74]. Imaging studies of the basal ganglia during motor movements demonstrate bilateral activation of most subcortical areas. Roland et al. (1982) had subjects perform a finger opposition paradigm and examined the subcortical activation using PET [75]. The results noted a strong contralateral signal increase (30%) and a weaker ipsilateral signal increase (14%) in the globus pallidus. The head of the caudate also had a bilateral increase (11-15%) as well as the putamen (15%) and the thalamic-subthalamic region (10%). Roland noted that bilateral activation of all structures except the primary motor cortex is remarkable, since the finger movements were strictly unilateral. Roland's work, along with other imaging research that will be reviewed later, suggest that the subcortical motor system is integral to the production of movement and the learning of movement sequences. Fundamental questions regarding how this system works are

now being addressed, and recent research has expanded our understanding of the neuronal architecture which drives this complex system.

A conceptual framework for understanding the extensive and complex subcortical network was proposed by Alexander, Delong and Strick. In 1986, they provided a comprehensive review of the subcortical motor circuit and its functional significance. A brief review based on this article follows [67]. The motor circuit is largely centered on the putamen, which receives substantial, somatotopically organized projections from the motor and somatosensory cortex. Both the motor and somatosensory cortical "leg" areas project to a dorsolateral sector of the putamen, the "face" areas to a ventromedial sector, and the "arm" areas to a region in between. In addition to the motor and somatosensory projections, the putamen receives topographically organized projections from area 5, from lateral area 6, including the arcuate premotor area, and from the supplementary motor area. The putamen sends topographically organized projections to the ventrolateral two-thirds of both the internal and external segments of the globus pallidus and to the caudolateral portions of the substantial nigra. The portion of the internal pallidal segment that receives putamen input projects in turn to the oral part of the ventrolateral nucleus of the thalamus (Vlo). The Vlo projects to the supplementary motor area. Somatotopically organized projections from the supplementary motor area, the arcuate premotor area, motor cortex, and the somatosensory cortex descend through the motor circuit to ultimately converge on a single cortical area, the supplementary motor cortex. As discussed, the supplementary motor area is important for motor programming and execution. The supplementary motor cortex projects to the primary motor cortex, arcuate premotor

area, and directly to the spinal cord where it may directly synapse on spinal motoneurons in a fashion analogous to descending fibers that originate from the primary motor cortex. It is also noted that the putamen and the globus pallidus appear to be somatotopically organized. The role of this subcortical motor circuit may be in the control of movement direction and in the scaling of movement amplitude or velocity. It appears that the basal ganglia activates after the cortical motor area in relation to stimulus triggered movements suggesting that the basal ganglia receives a copy of the movement program that allows it to influence the 'buildup of muscular activity in the first agonist burst and thereby participate in the control of movement speed and amplitude" (p.366)[67]. Important to the current study, the subcortical motor circuit may also play a role in the programming and initiation of internally-generated movements and in the preparation for movement [76].

Strick, Dum and Picard (1995) provide an expanded interpretation of the prior model based on recent findings that the frontal lobe contains multiple areas involved in the generation and control of limb movement including the SMA proper and pre-SMA areas [77]. Their research suggested that each cortical area preferentially projected to a topographically distinct region of the caudate and putamen. In return each cortical region appears to receive projections from topographically distinct regions within the internal segment of the globus pallidus. This arrangement leads to multiple "closed loops" and each of the six premotor areas in the frontal lobe may have its own unique loop. Strick, Dum and Picard investigated these hypotheses noting that pallidal neurons that were preferentially active during the performance of remembered sequences of movement were located dorsally in the internal segment of the globus pallidus, within

the output tract that leads to the SMA. They suggest this loop may be involved in the guidance of movements based on internal cues or determining the serial order of motor behavior or both. Conversely, pallidal neurons that were active during the performance of sequences of movements guided by external cues were located ventrally in the internal segment of the globus pallidus, a regions that projects to the ventral or lateral premotor area. They suggest this loop may be involved in the guidance of movement based on external cues [77].

Alexander and DeLong (1985) also reported on the idea that the subcortical motor circuit may be subdivided into functionally defined areas based on "an individual body part or even a specific movement of an individual body part" (p. 367) [78]. Involuntary movements or impairments of movements of a single body part such as monochorea, focal dystonias, or focal dyskinesias, may result from isolated lesions or aberrations within these areas. Studies addressing the manifestations of lesions in the subcortical motor system illustrate the role these systems play in the control of motor output and provide fodder for new hypotheses regarding this system.

Marsden (1987) puts forth an interesting hypothesis to explain the motor anomalies seen with diseases such as Parkinson's and Huntington's [79]. Marsden speculates that the basal ganglia in humans is concerned with the accurate execution of complex movements requiring simultaneous or sequential operation of separate motor programs. The output of the basal ganglia is likely to be directed at the supplementary motor area and the lateral premotor area based on the similarity of deficits produced with lesions of the supplementary motor area and the deficits seen in Parkinson's patients. Marsden further speculates that perhaps the motor basal ganglia are really

more concerned with directing what happens to the next movement in a sequence than with the initial movement. The basal ganglia may receive a copy of the motor program via corticostriatal pathways from the primary motor cortex that initially drives the movement itself. The putamen and globus pallidus fire in relation to the direction and amplitude of the movement. The basal ganglia then monitors parameters of the movement using this information to subsequently set up the parameters for the next movement. The motor defects seen in Parkinson' s and Huntington's disease may be related to the idea that in order to execute a correct single movement, the information regarding the current motor state must be relayed to the premotor area. If the information regarding the existing motor activity from sensorimotor cortex delivered to the basal ganglia is "mishandled," the output of the basal ganglia to premotor areas might misdirect the selection of the parameters for even a simple single movement and thus produce a movement error.

Based on the prior discussion, the basal ganglia plays a complex role in the formation, regulation and execution of motor programs [67]. The exact mechanisms by which these effects occur are still not completely understood; however their importance is only highlighted by the physical findings seen in patients with disease of these subcortical structures [79]. The fundamental role of the basal ganglia in volitional, executed movements is quite clear; however, the role these structures play in motor imagery is just beginning to be addressed. As will be discussed in detail in later sections, the basal ganglia are among the many motor system structures (eg., SMA, parietal and primary motor cortex) that are implicated in motor imagery and learning [80]. A hypothesis generated during the execution of this experiment is that imagined

motor practice will be able to access the basal ganglia to refine and restructure the motor program just as executed practice utilizes this system. The imagined sensory input may interact with the basal ganglia to develop and refine the motor program, which is subsequently sent to the SMA for effectuation. These ideas are speculative and this review will later address the substrate of imagery in greater detail. Future research studies will be able to address these questions directly.

The following section reviews recent functional and physiological studies that have addressed motor system organization. Not only is the fundamental localization of function important, but an understanding of the fidelity of our imaging techniques is necessary if we are to trust the results of these studies. As such, we review several works that have attempted to compare the results of functional imaging with more traditional "gold standard" techniques of assessing cortical function; namely intraoperative stimulation mapping. The section concludes with several examples of the promise fMRI holds the in the field of Neuroscience as it applies to human motor function. Because the resolution of fMRI is improving each day, we are now able to document functional activation with greater accuracy and higher resolution than ever before.

Functional MRI Studies of Motor Movement

Our study proposes to use functional MRI to investigate the role of motor imagery and its effects on cortical representations. Functional MRI is a relatively new modality for investigating the neurophysiologic basis of motor performance. Recent experiments using functional MRI have attempted to replicate the classic motor system studies that were originally investigated using PET and other techniques. At this time it

is appropriate to review the functional MRI studies that have looked directly at motor system function as well as examine some of the motor studies that have been done to document changes that occur as the direct result of diseases affecting the motor system.

Initial studies of motor function originally used simple finger tapping experiments to image motor cortex. Rao et al. (1993) were among the first group of investigators to use a complex finger tapping paradigm in fMRI experiments [81]. Subjects in this study performed a repeated fixed sequence of finger tapping. Complex, self-paced movements activated the contralateral primary cortex, occasionally the ipsilateral primary motor cortex, the supplementary motor cortex, the premotor cortex bilaterally, and the contralateral somatosensory cortex. These findings are similar to those reported by Roland et al. (1980) in which they noted a difference in the spatial distribution of brain activation during the execution of simple vs. complex self-paced movements [57]. Kim (1993) corroborated these findings, noting that right primary motor cortex was activated primarily by contralateral finger movements, whereas the left motor cortex was activated by both ipsilateral and contralateral movements [82]. The effect was more pronounced in right vs. left handed subjects, suggesting a relationship between ipsilateral motor control and degree of hemispheric specialization. Boecker et al. (1994), using unilateral middle finger tapping, found contralateral primary motor, contralateral primary sensory cortex, bilateral supplementary motor, and inconsistent bilateral or unilateral lateral premotor activation [83]. In addition to their findings during self-paced movements, Rao et al. also noted activation of the premotor cortex during imagined movements, suggesting a role for the premotor cortex in the

planning and execution of complex movements [81]. The topic of imagined movements and motor imagery will be revisited in the next section.

At about this same period, clinician investigators began trying to correlate functional MRI studies with invasive cortical mapping to assess the fidelity of functional imaging maps. Epilepsy patients provide a suitable subject population for these types of studies because they typically are healthy and undergo invasive mapping as a routine part of their care. Jack et al. (1994) presented a case report of two patients who underwent both functional MRI studies and invasive cortical mapping at the time of epilepsy surgery [84]. Subjects performed bilateral finger to thumb opposition and contraction-relaxation of the lip and lower face muscles. Volume renderings were generated and visually compared to the results of intra-operative cortical stimulation mapping. Results from this preliminary study indicated that the two mapping procedures were highly correlated and provided a possible non-invasive means of mapping patients prior to surgery. Youssry et al. (1995) provided corroboration of the findings reported by Jack, showing that fMRI in six patients with tumors involving the motor cortex had fMRI signal activation in the vicinity of the rolandic cortex [85]. Youssry et al. note that intrasurgical electrical stimulation of the motor cortex in areas that corresponded to increased signal intensity on functional MRI resulted in motor responses from the contralateral hand muscles. A third contribution was reported by Chapman et al. (1995) in a study comparing invasive monitoring and fMRI in a pediatric patient with a tumor in the dominant supplementary motor area who presented with seizures [86]. Self-paced repetitive opening and closing of the right hand activated primary motor cortex and cortical stimulation caused involuntary flexion of the right

thumb, finger, and wrist flexors. Latchaw et al. (1995), using sequential finger tapping, also found a similar pattern of activation in primary motor cortex in a patient with an arteriovenous malformation [87]. The fMRI map was used to plan the surgical excision and the patient awoke post-operatively without any deficit. Kahn et al. (1996) also used fMRI to map the hand area before using MRI-guided laser-induced interstitial thermotherapy for brain tumors [88]. They found similar patterns of activation; however, some tumor patients displayed a less focal or scattered appearance with the activation map covering a larger region. Kahn et al. speculate that the changes were the visual proof of cortical reorganization and emphasized the need for pretherapeutic localization of the cortical motor area in patients at risk for deficits. Morioka et al. (1995) provided evidence that fMRI not only correlates with intraoperative mapping, as discussed, but also correlates with other non-invasive functional mapping techniques [89]. Functional MRI was compared to magnetoencephalography, and motor evoked potentials in a patient with a sensorimotor cortex lesion. Morioka reported of that all three techniques demonstrated good agreement between the location of the sensorimotor cortex and its relationship to the lesion. Together these studies provide convincing evidence that fMRI activation seen on post-processed images accurately represents the underlying functional organization of the cortex.

It appears that functional MRI is not only capable of imaging large cortical regions, but the resolution is high enough to subdivide regions based on functional specialization. Rao et al. (1995) addressed this issue by having subjects perform right arm, foot, and elbow movements during an fMRI experiment [90]. The findings demonstrated that the patterns of functional activity followed a topographic

representation with right finger movements eliciting action over the left convexity, toe movements producing activation in either the interhemispheric fissure or the dorsolateral surface adjacent to the interhemispheric fissure, and elbow movements causing activation that overlapped more medial signal changes seen with finger movements. These findings corroborated a prior studied by Wasserman et al. (1992) that used transcranial magnetic stimulation to map muscle representation in the motor cortex [91]. Wassermann et al. reported mapping a somatotopic progression on the scalp of proximal to distal muscles along a "posteromedial to anterolateral axis." Additional studies have used the high spatial resolution of fMRI to further subdivide the motor cortex, even calling into question the early views of human M1 region organization. Penfield and Boldrey placed proximal movement representations medially and those for successively distal movements in discrete, non-overlapping regions in the lateral part of the representation [12]. Sanes et al. (1995) used fMRI to demonstrate that there are shared neural substrates controlling human hand movements [92]. Sanes et al. identified a distributed, overlapping pattern of hand movement representations within the posterior precentral gyrus. Finger and wrist movements activated a wide expanse of the posterior precentral gyrus, and representations for different finger movements overlapped each other and the wrist representation. The area activated by thumb movements overlapped with 68% of the index finger, 60% of the ring finger, and 53% of the wrist representation. Porro et al. (1996) also found multiple independent foci activated within the precentral gyrus noting that these areas probably "represented overlapping areas controlling distal movements" (p. 7695) [6]. Based upon their results, Sanes proposed a working hypothesis that neurons within the

M1 area form a "distributed and cooperative network that can simultaneously and optimally control collections of arm muscles, and these results concomitantly provide further evidence against the hypothesis that the M1 area contains single, discrete or topographically organized regions for finger or wrist control" (p. 1776) Sanes' findings seem to overestimate the spatial resolution and repeatability of the functional MRI technique, especially in 1995; none the less, the concepts proposed are intriguing and warrant discussion. Sanes' findings provide an introduction to the idea that neural elements or ensembles that make up the functional processing units may continually recombine while forming new output properties to produce normal and adaptive motor behavior. Overlapping movement representations may form an adaptive and dynamic network to mediate complex motor and cognitive phenomena. The ability to acquire new or advanced motor skills may use the overlapping distribution in its favor. Nudo has shown in animals that motor learning occurs by adjacent cortex expanding into neighboring distributions [93]. The interconnectivity of task-related regions in the motor cortex may facilitate reorganization and by extension learning.

As discussed, early fMRI work was able to replicate many of the hallmark findings produced using invasive functional imaging techniques such as PET. Functional MRI has found favor among the research community because it is non-invasive and offers improved quality and resolution over older techniques. Since the images obtained with functional MRI represent changes in signal resulting from blood oxygenation changes, it has been important to correlate fMRI with more traditional techniques such as intraoperative stimulation mapping. As the review noted, the gold standard of intraoperative stimulation mapping has a very high fidelity with fMRI

motor maps and this coincidence has lent further credibility to the technique. With the capacity for high resolution imaging, researchers are now beginning to study the subrepresentations and networks that are within the traditional boundaries that segregate functional motor areas. In addition to providing activation maps of the primary motor cortex, fMRI has given us a better understanding of some of the subcortical and higher order motor systems. With continued improvements in resolution, fMRI has expanded our knowledge of the role subcortical structures play in volitional movement. Functional MRI also holds promise for investigating the substrate that controls motor learning and motor imagery, since researchers believe these tasks may involve the same neuronal pathways as volitional motor sequence planning and execution.

Volitional Movement Summary

Based on our knowledge of the fundamental mechanisms supporting movement, we are now better able to understand how motor imagery might utilize systems designed for the production of movement. We know that subcortical structures integrate tremendous amounts of information to create the motor program and that these same areas are responsible for feedback control of motor output. Likewise, we know that the performance of tasks can be cued by internally generated signals from the medial prefrontal cortex. We also know that the basal ganglia can address the primary motor cortex via the supplementary motor cortex to run motor programs requiring skilled use of the digits. It seems logical that this highly organized and rehearsed system would not be duplicated for processes that require similar output, such as motor imagery. In the next section, the conceptual framework surrounding imagery theory

and current research findings that suggest motor imagery utilizes that same neural substrates as executed, volitional movement will be discussed.

Imagery

The prior discussion was devoted to the neural circuitry implicated in volitional, executed movement. Our interest in this project is to examine the role imagery plays in improving motor performance and correlate motor improvement with changes in cortical representation. Pragmatist theories have emphasized the functional character of ideas, noting that ideas are suggestions and anticipations of possible conduct; they are hypotheses or forecasts of what will result from a given action. Decety (1996) notes that motor imagery could be a way to "assess the physiological substrate of the transformation process between intention and action [94]. Along those lines, it has been said that "a subject is imaging whenever he employs the same cognitive processes that he would use in perceiving, but when the stimulus input that would normally give rise to such as a perception is absent" (p. 62) [80]. Crammond (1997) suggests that motor imagery is something "quite separate from the creative imagination, which is not so easily shackled" Crammond notes that "we can only mentally rehearse doing something that we have done before, and only as we experience it in practice" (p. 56) [95]. It seems likely that the cerebral substrates for images and percepts may be intimately related and jointly accessed during motor imagery. Cohen et al. (1996) note "data strongly support a sort of conservation principle of mental events: that the machinery of primary sensation, imagery, and perhaps perception might well be the same" (p. 97) [96].

Multiple studies have been performed addressing the mechanisms and neural substrate underlying motor imagery. To understand the underlying neural components of motor imagery, we must first define motor imagery and explain how motor imagery is attempted by human subjects. Motor imagery can be defined as the mental rehearsal of simple or complex motor acts that are not accompanied by overt body movements [6]. Annett (1996) proposes a theory that motor imagery "contains two elements, firstly the activation of the action prototype and second, memories of the perceptual consequences of previous actions of a similar kind" (p. 67) [97]. The first element is shared with overt action while the second is a substitute for the sensory feedback which would normally arise from the overt action.

Two types of mental representations of motor acts can be generated by normal subjects: an "internal" or first person process in which subjects feel themselves executing movements, and an "external" or third-person process involving a visual representation of actions [3, 98]. Unlike external imagery, internal imagery is difficult to describe verbally but subject's responses are characterized by descriptions of vivid mental representations and changes in heart and respiratory rates that are related to the degree of mental effort [99]. Internal imagery is the most common type of imagery employed in the research surveyed here, and is the type of imagery employed in this project.

A review of the imagery literature finds that the debate on imagery has centered on two issues. The first is whether the neural substrate responsible for imagined movement is equivalent to the substrate responsible for volitional, executed movement. The second is whether primary motor cortex is involved in motor imagery and if so,

how is movement prevented through inhibitory mechanisms. These two issues will be addressed in turn and the relevant functional imaging research on the topic of motor imagery will be reviewed.

It has been vigorously debated whether the neural substrate responsible for imagery is the same as the underlying neuronal pool that facilitates volitional, executed movements .[Converging evidence suggests that motor imagery uses the same types of processes as those involved in programming and preparing for actual movement. The difference between volitional movement and imagery is that in imagery execution is blocked at some level of the corticospinal output pathway.] Decety (1996) provides a comprehensive review of motor imagery suggesting that motor imagery requires a serial (sequential) organization of cortical neuronal events [94]. The timing of mentally simulated movements occurs in a hierarchical fashion originating from higher levels than that from which motor execution is controlled. [Motor imagery is thought to be controlled by the prefrontal and dorsolateral prefrontal cortex which, according to Decety, are specifically involved in carrying out the "computations of the action programming subsystems which deal with planning at the coarsest level"] (p. 50). The coarsest level being the timing of cognitive and motor events. Prefrontal cortex, as discussed, is necessary for regulating behavior guided by representations or internalized models of reality. Premotor cortex is implicated in the retrieval of movement. Prefrontal and premotor cortex are usually activated in motor imagery studies and their participation seems logical in light of the role these areas play in the execution of volitional movement. Petsche et al. (1996) reported on the EEG aspects of mentally playing an instrument, concluding that significant changes of coherence emerged from

electrode Fz, the supplementary motor electrode, while imaging playing music [100]. Decety also implicates attentional processes as likely participants in motor imagery [94]. She notes that both anterior and posterior attentional systems, including the medial prefrontal, anterior cingulate, supplementary motor, and the lateral parietal cortex, play a role in motor imagery. These areas control motor imagery through their involvement in executive control, working memory, preparing responses, and the conduction of operations such as disengaging, moving and the engaging of attention. As discussed, parietal lesions lead to impairment of skilled movements resulting in apraxia. Based on these findings, it is suggested that parietal cortex is important for storing and accessing motor representations [65]. Sirigu et al. (1996) studied mental representation of hand movement after parietal cortex damage [101]. Patients with lesions restricted to the parietal cortex were found to be impaired selectively at predicting, through mental imagery, the time necessary to perform differential finger movements and visually guided pointing gestures. These results suggest that the parietal cortex is important for the ability to generate mental movement representations. Tootell et al. (1995) noted that the perception of motion, even illusory motion, is correlated strongly with increased activation of V5/MT as seen using fMRI [102]. Cohen et al. (1996) surmised that the neural machinery for mental rotation is likely the same as direct perception utilizing cortical regions typically involved in detection and analysis of form and motion [96]. Sirigu hypothesizes that kinesthetic representations stored in parietal cortex must first be activated and organized to entrain other brain regions that are active during movement stimulation. Sirigu further speculates that the parietal cortex is involved in monitoring the motor outflow, through the "efference

copy received from downstream motor areas". In addition to the cortical areas discussed, both cerebellum and subcortical structures are likely participants in the production of motor imagery.

The role of subcortical areas in the production of volitional movement has been discussed. Under the current general hypothesis that imagery and volitional movement share the same basic neural network, we would expect to see involvement of subcortical structures during motor imagery. It seems likely that the basal ganglia play a role in the control of the internal state at least as far as motor production is concerned. Dominey and Arbib (1992) suggests that frontostriatal pathways are involved in the control of the internal state, and allow for the transition between internal states that encodes sequential vs. non-sequential movement execution [103]. The cortico-pallido-thalamo-cortico loops discussed by Alexander et al. (1986) may provide the anatomic pathways for the state transition mechanism [67]. Based on these findings, we might expect that patients with disease of the subcortical structures would manifest difficulties on motor imagery tasks. In fact, Saint-Cyr et al. (1994) demonstrated that the internal state control necessary for sequential procedural learning is impaired in Parkinson's disease patients [104]. Based on these studies and others, frontostriatal dysfunction likely affects the internal representation (imagery) and external expression (movement) in parallel. Decety speculates that the basal ganglia "not only responds to the internal state, but also participates in maintaining the internal state, and in controlling the orderly succession of transitions from one state to the next" (p. 50) [94]. Decety (1991) found that PET activation increased bilaterally in the caudate nucleus and premotor cortex during motor imagery but not during observation of a motor task [99]. Roland et

al. (1982) found bilateral activation in the basal ganglia during sequential finger movements, suggesting that the basal ganglia is not only involved in the initiation of movement, but is likely involved in the control of internal state during sequential movements [75].

It is interesting to speculate that if mental imagery shares the same basic neural components as volitional movement, then dynamic physiologic changes might be expected to occur in response to mental imagery. Several studies have addressed this issue. Decety et al. (1991) measured cardiac and respiratory activity during actual and imagined movement, finding a covariation of heart rate and pulmonary ventilation with the degree of mental effort [99]. Beyer et al. (1990), evaluating the same two variables, found that in a group of subjects requested to imagine swimming over a distance of 100 meters, respiration frequency doubled during motor imagery as compared to breathing at rest [105]. Heart rate increased 30% over resting conditions. Based on these findings and other similar reports in the literature, Decety speculates that the visceral changes noted in response to motor imagery are likely of central origin. Decety conducted another experiment to assess this hypothesis, using heart-lung transplant patients [94]. When heart-lung transplant recipients performed motor imagery, using similar paradigms as discussed, no cardiovascular response was obtained. Since these patients have denervated hearts, this result suggests that the origin of the response in normal subjects is centrally mediated. It seems clear that physiological changes occur in response to motor imagery, thus lending credibility to the idea that imagined movements share the same basic neural connections as volitional movement.

Functional imaging researchers have investigated the basis for shared neural connectivity during executed and imagined movements. Ingar and Philipsson measured regional cerebral blood flow (rCBF) during imagined slow, rhythmic hand clenching and demonstrated increases in premotor and frontal regions [106]. When only hand movement was performed only the contralateral primary motor cortex showed increase blood flow. Roland et al. had subjects imagine performing rapid and "skilled" sequences of digit movements and found supplementary motor activation [57]. These results suggest the importance of SMA for internal programming and simulation of complex motor sequences. Other regions commonly seen during imagery include the anterior cingulate cortex, which is implicated in the attentional mechanisms necessary for attention-requiring tasks such as executive control, working memory, and preparing responses; the cerebellum, which has extensive connectivity with frontal and parietal cortex ipsilateral to the side of imagined movement; the basal ganglia and the parietal cortex, which is also implicated in attentional mechanisms [107, 108].

Important to the current study is the finding that in addition to motor association cortex, primary motor cortex has been found to activate during motor imagery. Roth et al. (1996) studied both actual and mental execution of a finger to thumb opposition task using fMRI [109]. They noted involvement of the contralateral M1 during both imagery and execution of their task. It was noted that the activation during imagery was about 30% of the activation seen during execution; however this was significant. They suggest that their findings are consistent with reports in the animal literature that neurons in premotor as well as in M1 can be active during preparation for action, with no movement resulting. These findings are supported by Tyszka et al.(1994), who

found primary motor cortex activation in addition to supplementary motor and anterior cingulate cortex activation during imagery [110]. Porro et al. (1996) used fMRI to study cortical activation during motor imagery and compared the finding to the execution of volitional movements [6]. Subjects in this study were instructed to "imagine using the right hand to perform movements and feeling the sensations associated with finger-tapping, while keeping the hand still" (p. 7689). They used video monitoring to ensure that no overt movement occurred during the imagery portion of their study. Results demonstrated that significant increases in signal activation were found in regions including the anterior bank and crown of the central sulcus during both motor performance and motor imagery. The mean percentage signal changes for performance and imagery were 2.1% and 0.8%, respectively. The finding by Roth et al. (1996) that imagery produced about 30% of the activation seen during motor execution was reproduced in the study by Porro et al. [6]. Porro et al. concluded that "pixels activated during both motor performance and motor imagery appear to represent a large fraction of the whole population activated during motor performance [alone]" (p. 7688). These studies support the hypothesis that motor execution and motor imagery share an overlapping neural network in the perirolandic cortical area. An interesting ancillary finding by Porro suggests that the observed fMRI changes noted in the postcentral gyrus during motor imagery may be related to somatosensory imagery. Recall that in their study subjects were asked to recall the sensations associated with finger tapping. The implication is that motor imagery may involve both exteroceptive and proprioceptive components. It is common to see the post-central gyrus activated during fMRI studies of overt motor production. Thus the finding of

sensory cortex activation with imagery seems logical since imagery requires not only imagery of the motor component but also the sensory component of movement as well.

In addition to using functional imaging techniques to obtain static images of activation during imagery, the temporal sequence of these events has been investigated using MEG. Deecke, Weinberg, and Brickett (1982) reported on the concept of Bereitschaftspotential, or readiness potential, which is a cerebral discharge noted one or two seconds prior to the onset of EMG during voluntary movement [111]. They report that the SMA precedes the primary motor cortex in the "final motivational cascade before the execution of a motor action." Deecke further suggests that the frontocentral cortex including SMA is responsible for the intention or the "channeling of motivation" into the execution of movement. These findings support the general hypothesis that imagery may evoke activation of the supplementary motor cortex prior to M1 activation. The concomitant use of TMS and/or MEG may lead to a better understanding of the temporal components of the activation patterns noted on PET and fMRI studies.

Neurophysiologic studies using TMS have attempted to provide evidence that motor imagery can facilitate motor-evoked potentials. It has been shown that the excitability of motor pathways, as tested using TMS, specifically increases during mental simulation and that mental training increases the area of motor cortex from which the trained movement can be elicited. Lang and colleagues found that M1 is active during internal simulation of movements [112]. Lang et al. speculate that activation of movement and inhibition of movement may be mediated by excitatory M1 activity. Pascual-Leone et al. (1995) used TMS to show that after five days of mental

practice of a five-finger piano exercise, the cortical motor output maps targeting finger flexors and extensors enlarged, and their activation threshold decreased [113]. Kasai and colleagues have demonstrated that motor imagery can selectively activate corticomotoneuronal cells projecting to α-motoneurons without affecting the H-reflex [114]. Kasai also concludes that motor imagery changes the overall excitability at the cortical level and speculates that agonist and antagonist muscles are facilitated during motor imagery. Abbruzzese et al. (1999) also addressed this issue, looking at changes of cortico-cortical inhibition and facilitation during mental simulation of sequential finger movements in normal subjects [115]. The authors speculate that the modulation of cortico-cortico inhibition occurring during motor imagery strongly suggests that the inhibition is within cortical structures. Abbruzzese et al. conclude that the "similarities in the behavior of cortico-cortico inhibition during mild voluntary contraction and motor imagery might suggest that the same 'downregulation' of intracortical inhibitory mechanisms operates during motor programming, although the released motor program is more or less inhibited somewhere on its way to peripheral effector organs" (p. 115). In an early paper, Abbruzzese et al. [116] found evidence to support the findings of Kasai et al. [114], suggesting the combination of agonist and antagonist activity in motor cortex did not translate to spinal cord level excitability as detected using the H-reflex. The mechanism by which motor imagery is inhibited from being translated into executed motor movement is unknown; however Bonnet et al. (1997), having found evidence of weak EMG activity during mental imagery, speculates that recurrent inhibition at the spinal cord level could be the mechanism utilized by descending

pathways to reduce the number of motoneurons activated during motor simulation [117].

It seems clear from the prior discussion that motor imagery is modulated in a similar fashion to volitional movement. Similar cortical and subcortical areas are active during either imagery or action. Likewise, both imagery and motor expression cause compensatory autonomic responses suggesting a central role for both processes. This review supports Cohen et al. (1996) who noted "data strongly support a sort of conservation principle of mental events: that the machinery of primary sensation, imagery, and perhaps perception might well be the same" (p. 97) [96].

While motor imagery is one component of this research, an equally important component is the concept of motor learning. In the next section, the concept of procedural learning and the contemporary theories regarding the localization of this process will be addressed. Many authors suggest that the substrate used for both volitional movement and motor imagery is the same as that utilized for procedural learning. Again the concept of conservation of resources is applied.

Procedural Learning

Procedural knowledge is generally used to refer to a form of knowledge which can be measured by tasks in which memory is expressed by changes in performance as a result of prior experience [118]. Procedural knowledge has been applied particularly to the acquisition of actions, habits, and skills. Procedural knowledge can be either explicit or implicit. Explicit and implicit knowledge refers to whether a subject has a conscious awareness of exposure to a task or information that eventually results in improved performance. An example of explicit-procedural knowledge might be a

situation where a subject deliberately aims to improve his/her performance on a task by repeatedly having exposure to it.

Theoretical models for procedural learning closely parallel the mechanisms discussed for volitional and imagined movements. Vogt (1996) suggested that imagery of a movement sequence exerts similar learning effects as physical and observational practice, and visual and motor imagery are equally effective rehearsal strategies for maintenance of temporal information in short-term memory [119]. These hypotheses support the general principle that the neural substrate controlling volitional movement is conserved across tasks that have movement, either real or imagined, as the ultimate goal.

Pascual-Leone et al. (1995) provide an extensive review of procedural learning and the structures implicated in the production of these constructs [118]. The author studied patients with diseases that affect motor function as a means of defining where procedural learning is modulated in the brain. Several structures are implicated in procedural learning, one of which is the basal ganglia. Serial reaction time tests conducted on patients with Huntington's disease, progressive nuclear palsy and Parkinson's disease were abnormal, suggesting deficits in explicit knowledge accompany these diseases. Pascual-Leone et al. argue that the necessary "energizing" influence of the basal ganglia on the prefrontal cortex is deficient in Parkinson's disease, resulting in abnormally slow access of information to and from "working memory" buffers.

Selective impairment of procedural learning has also been reported in patients with cerebellar dysfunction. The lack of acquisition of procedural knowledge is linked

to the absence of the normal modulation of motor cortical outputs to the muscles involved in the task. Pascual-Leone argues that intact cerebello-cortical interaction is required to induce the plastic changes normally associated with procedural learning. Conceptually, the cerebellum may be required to provide a time index to the events in a serial reaction time test. Interestingly, the role of the cerebellum is lateralized and selective for procedural learning with the hand ipsilateral to each cerebellar hemisphere. From this discussion, the cerebellum in addition to the basal ganglia seem to be critical structures necessary for the development of procedural knowledge.

The third structure seen as critical to the development of procedural knowledge is the dorsolateral prefrontal cortex. The dorsolateral prefrontal cortex is highly interconnected with both the cerebellum and basal ganglia. Passingham discusses that the major input to the lateral premotor cortex comes from the parietal association cortex, specifically area 5 and area 7b [60]. He suggests that information is transferred about the position of the limbs and jaw, and the expression of the face. This information is coded in proprioceptive coordinates and is especially important when individuals must select between movements. Stimulation of dorsolateral prefrontal cortex leads to an apparent block of procedural learning when performed by the contralateral hand [118]. Pascual-Leone et al. argue that prefrontal structures integrate input from the basal ganglia and cerebellum providing "the critical aspect of sequencing events in time, bridging temporal contingencies between individual trials, and thus provides the subject with the basis for recognizing the sequential nature of the task" (p. 67). From this discussion, it appears that three critical areas exist that facilitate procedural learning, namely, the basal ganglia, cerebellum and the dorsolateral

prefrontal cortex. While these structures likely play a major role in the modulation of motor learning, other factors are in play to produce the final product of improved performance. A critical factor is the ability of the motor cortex and its associated structures to undergo changes as a result of the influences exerted by the structures involved in procedural learning.

Procedural learning induces changes in cortical representations in specific patterns related to the muscles involved in the learned task. Pascual-Leone et al. (1994) used a serial reaction test to allow subjects to develop implicit knowledge of the test sequence as reflected by diminished response times [120]. Cortical mapping with TMS revealed that the cortical representation of the muscles involved in the task became progressively larger until explicit knowledge was achieved. Interestingly, after this point the cortical representations regressed to their original size. As noted, the changes seen in this study likely developed based on a neural network that includes critical contributions from the cerebellum, basal ganglia, and prefrontal cortex. The return of the maps suggests that as a motor sequence is explicitly learned, the contribution of the motor cortex is attenuated and other brain areas assume more active roles in the execution of the task. The author notes that the dorsolateral prefrontal cortex is implicated as playing a major role in the integration of neural information from both the cerebellum and basal ganglia during the implicit procedural learning processes, but activation may shift to the striatum as motor sequences are committed to explicit memory.

Beyond defining the anatomic location of procedural learning, it is interesting to note that changes in the location of activation occur as new tasks are learned and

committed to memory. Pascual-Leone et al. speculate that as tasks become highly refined the activation of the primary motor cortex is less pronounced and the basal ganglia begins to direct the automated task. Likewise, it is interesting to note that the consolidation of skilled motor performance is not immediate and these shifts in activation may occur over time. This hypothesis seems logical since by experience we know that complex skills are learned over days and weeks, not minutes or hours. The acquisition and consolidation of skilled motor performance occurs over a variable time frame and these changes may result in significant experience-related reorganization within specific motor representations in the human brain. Additionally, these representational changes may occur in several stages and may be characterized by a distinct time course. Karni et al. (1998) investigated these hypotheses using a repeated finger tapping sequence practiced over three weeks [5, 121]. Functional MRI was used to study the changes in cortical represention as subjects performed finger tapping before and after three weeks of practice. Karni et al. [121] suggest that "skilled motor performance is acquired in several stages: fast learning, an initial, within-session improvement phase, followed by a period of consolidation of several hours duration, and then slow learning, consisting of delayed, incremental gains in performance emerging after continued practice" (p. 861).

The idea of using changes in cortical representations as a marker for learning is based on the concept of use-dependent plasticity in which intra-cortical connections are thought to be altered as a result of practice. The Karni et al. report [121] on the temporal evolution of acquired motor skills was based on a prior study that demonstrated enlargement of cortical representations following practice of a motor

sequence [5]. More recent studies suggest that cortical plasticity results in the expansion of representations and possibly the remodeling of gross anatomical landmarks after prolonged periods of motor learning. Pascual-Leone et al. (1995) in contrast to their earlier work [120], showed that over the course of five days as subjects learned a five-finger exercise on the piano, the cortical motor areas targeting the long finger flexor and extensor muscles enlarged [113]. Amunts et al. (1997) provided an example of cortical structural change associated with learned motor skills [122]. Measuring the intrasulcal length of the precentral gyrus (ILPG), Amunts et al. found the size of the ILPG was negatively correlated with age of commencement of musical training in keyboard players. Amunts et al. conclude that "the human motor cortex can exhibit functionally induced and long-lasting structural adaptations" (p. 206). While Amunts' findings are intriguing, his conclusions are not the only interpretation.

The exact mechanism for these gross structural changes are likely due to fundamental changes in the neurophysiologic properties of the neurons comprising the relevant cortical regions. The topic of cortical plasticity has gained much notoriety of late, largely due to new insights gained by functional imaging techniques. As discussed, increased cortical representations with motor learning have been noted , as well as other alterations in cortical activation following injuries and stroke. It is likely that plasticity, when used as a general term, is the foundation for most of the processes involved in learning and consolidation of memories. While the increased activation noted on imaging represents the summation of neuronal activity, the underlying mechanisms for reorganization likely include alterations in synaptic properties, the formation of new synapses, or the recruitment of additional adjacent or remote cortical

areas. The next section will review both the larger changes noted with imaging and the fundamental changes that are occurring on the synaptic level.

Plasticity: Implications for Motor Skill Learning

Throughout life the functional properties of the nervous system remain inextricably linked to the influence of new experience. The neural circuitry of the brain remains malleable, retaining the ability to undergo significant reorganization or plasticity. These changes can occur as a result of lesions to the motor system or as a result of practice and experience. Many investigators have described alterations in cortical representation as a result of motor practice. Among them, Karni et al. (1995) demonstrated, using fMRI, that motor practice can enlarge cortical representations [5]. Similarly, Elbert et al. (1995), using magnetic source imaging, reported that string players had increased cortical representations of the fingers of the left hand [123]. Both investigations concluded that the cortical territory responsible for the studied movement expanded as a direct result of practice.

These findings are important but it is likely that changes in brain organization occur more readily in some populations than others. Most imaging studies are performed in adults; however, it is likely that the ability of the brain to undergo plastic change is somewhat age dependent. Children are able to learn more readily than adults and are able to recover from devastating cortical injuries far more readily than adults. Recent imaging studies show that adults do manifest evidence of cortical reorganization during learning exercises and following injury. In fact, these changes have been documented in the oldest of patients studied. The factor that is likely the rate-limiting and age-limiting step is the cortical and cellular mechanisms responsible for neuronal

plasticity. It is likely that synaptic and cellular changes determine the time course of skilled learning and the potential for recovery after an injury. These concepts have huge importance for this research and have broad implications for the field of neurorehabilitation. The likelihood is that all research utilizing imaging ultimately is founded on the changes that occur at the synaptic and cellular level; imaging may only be a reflection of these events particularly when evaluating learning or recovery after brain injury. Recent studies have been done to investigate the patterns of cortical reorganization in primates and humans and to understand the cellular and synaptic mechanisms underlying these phenomena.

Several functional studies of humans who have shown cortical reorganization following performance of learned tasks have been cited. However, motor skill learning is not unique to humans, animals can show the same effects. Nudo and colleagues have contributed many important finding to this body of knowledge by discussing the cortical, subcortical, and synaptic mechanisms responsible for cortical reorganization in animals. Nudo et al. (1990) studied the effects of repetitive intracortical microstimulation on cortical representations in the rat [4]. Results demonstrated expansion of movement representations from 210 to 670 μm^2 following one to three hours of stimulus pulses delivered directly into the cortex. Interestingly, these border shifts were noted to be progressive and reversible. Nudo et al. speculate that the border shifts resulted from changes in the cortical circuitry itself or in subcortical motor structures. Importantly, Nudo et al. found that stimulation-induced changes are noted to occur in the absence of widespread direct activation of descending pathways. This is similar to what is reported for motor imagery [114, 116]. Nudo et al. also discusses the

time course of these changes, stating that "within a few tens of minutes following repetitive subthreshold intracortical microstimulation borders appeared to return to their prestimulation positions". Importantly, it was also noted that the "relative strength of output to various muscles represented at a given focus are continually modulated by prior activity at adjacent foci." This final statement lends credibility to the idea that adjacent cortical areas play a role in use-dependent plasticity. The speculation is that one cortical area, if used more than an adjacent area, can supercede control of the neighboring cortex and use the adjacent cortical area to facilitate the sought-after movement. This mechanism may be the driving factor to explain how cortical expansion occurs both in Nudo's studies and in the functional imaging literature.

Use-dependent plasticity is a fairly new concept that suggests that cortical reorganization can be forced by making subjects perform specific actions. Action, rather than direct cortical stimulation, can be used as a means of causing cortical activation. Nudo et al. (1996) investigated the concept of use-dependent plasticity, looking at changes in cortical representation in the squirrel monkey [93]. The research paradigm had monkeys trained on two tasks. The first task was the retrieval of small objects, a task that required skilled use of the digits at the exclusion of the wrist and/or forearm. The second task required pronation and supination of the forearm at the exclusion of the digits. The results indicated that the cortical area for the desired task expanded at the expense of the other areas studied. For example, digit use evoked digit representation expansion with concomitant contraction of wrist/forearm representations. The reverse was true if wrist/forearm tasks were performed repeatedly. A second finding was that after digit training there was an expansion of cortical regions that,

when stimulated, produced movements at two or more joints. Nudo et al. note that "movement combinations that were used more frequently after training were selectively magnified in their cortical representations" (p. 785). Nudo's conclusions suggest that co-contracting muscles in the behavior come to be represented together. The finding that "temporal correlations drive emergent changes in distributed motor cortex representations" supports earlier speculation that muscles represented at a given focus are continually modulated by prior activity at adjacent foci. As part of this study, Nudo et al. also performed repeated mapping during five phases of behavioral training that included the initial training period, an extinction phase where no training was conducted for four months, and a reacquisitions phase where the animal resumed training. Results from this portion of the study again suggest that use-dependent changes are progressive and semi-reversible. Interestingly, the reversal of the map was not complete after the extinction phase. Nudo et al. note that "although behavioral performance dropped to pretraining levels, finger representations decreased by relatively small amounts. This discrepancy between behavioral performance and representational area suggests that once a novel motor task is learned certain aspects of functional cortical topography remain altered for an extremely long period of time" (p. 804).

Cortical reorganization is not limited to situations of learning and repeated task performance. Injuries that affect the cortex can lead to reorganization as a means of compensating for lost function; however, reorganization left to its own devices may lead to further loss of function due to adjacent areas of preserved cortex recruiting cortex at the edge of the lesion nidus. If the areas recruited do not perform the same

function as the recruiter then reorganization may lead to a detrimental loss of performance from the recruited area as it is enslaved to perform the function of the adjacent cortical area. Nudo and Milliken (1996) addressed these issues, evaluating the degree of plasticity seen following motor cortex lesions in adult squirrel monkeys [124]. Following lesion placement, transient deficits were noted in the use of the contralateral hand on tasks requiring skilled digit use. Microstimulation mapping found widespread reductions in the digit representations with increased representation of proximal musculature. Spared distal representations also underwent continued retraction due to continued lack of distal limb movement. Based on these findings, Nudo and Milliken warn that the physiological consequences of cortical infarct are use-dependent and "spontaneous recovery by the assumption of lost function by adjacent, undamaged tissue is not inevitable" (p. 2147). New physical therapy modalities have taken heed of this warning by using techniques called constraint-induced therapy to force the preserved cortex to assume function of the impaired movements. For example, an individual can be forced to use a paretic limb to prevent adjacent cortex that may control axial musculature from superceding function from damaged cortical areas that may control distal extremity movement.

The use-dependent changes seen in animal studies and in human imaging experiments provide convincing evidence for the potential of cortical reorganization on a large scale. The changes in cortical organization that are discussed in functional imaging studies and other studies of electrophysiology are a secondary consequence of synaptic and cellular adaptation which provide the ultimately drive force for cortical reorganization. While functional MRI, TMS, and other studies provide gross evidence

of cortical change, the factors that allow the changes to be seen are observed on a finer scale. To fully appreciate how cortical reorganization occurs, we must briefly review the synaptic and cellular mechanisms that are the likely cause of these remarkable changes.

Review of Mechanisms Underlying Plasticity

The majority of speculation regarding the cellular mechanism responsible for learning and reorganization revolves around the concept of inducing long-term potentiation. A description of LTP and the mechanisms driving this phenomenon follow. Bliss and Lomo (1973) first demonstrated that a brief high-frequency train of stimuli to any one of the three afferent pathways to the hippocampus produced a subsequent increase in excitatory synaptic potential in the postsynaptic hippocampal neurons [125]. The increase in excitability was noted to last for hours to days or weeks. They termed this facilitation long-term potentiation or LTP. Later work has shown that LTP has different characteristics at different sites in the brain [2]. LTP in the CA1 region of the hippocampus has three properties that may be common to any learning process. First, LTP requires cooperativity to be generated. More than one excitatory connection must be made to induce LTP. Secondly, LTP is associative, meaning pre and post-synaptic cells work together in the generation of LTP. Thirdly, LTP is specific to the active pathway that generates it. While these characteristics were once thought to be specific for the CA1 region of the hippocampus, it is now general believed that these properties of LTP may be found, together or in part, in other areas of the brain including the motor cortex.

In 1990 Keller and colleagues identified neurons in the cat motor cortex that produce the LTP phenomena [126]. Keller's results demonstrated that both pyramidal and non-pyramidal cells in layers II and III of the motor cortex were able to produce LTP. The authors suggested that "various corticocortical inputs can increase the efficacy of synaptic transmission in a subset of motor cortical neurons" (p. 47) with the resultant plasticity in synaptic transmission possibly contributing to motor learning. Hess and Donoghue (1994) provided evidence that LTP can be induced in local intracortical connections providing a possible mechanism for synaptic plasticity in motor cortex [127]. Hess and Donoghue note that the occurrence of LTP in M1 horizontal fiber pathways demonstrates that activity in these intrinsic pathways can establish new, long-lasting associations among neurons distributed within a cortical area. It is thus assumed, that for motor cortex, the plasticity of intrinsic horizontal connections can assist in reorganization in response to lesions as well as "serve to adjust the synaptic coupling of distributed sets of M1 neurons to form representations that optimize performance" (p. 2546). Iriki et al. (1989) reported that associative LTP can also be induced in the thalamic input to the motor cortex by combined tetanic stimulation of the sensory cortex and the ventrolateral nucleus of the thalamus [128]. The authors suggest that the function of corticocortical LTP is to facilitate learning and retention of motor skills. During the slow phase of motor learning, LTP is transferred to ventrolateral thalamic nuclei as sensory feedback becomes less necessary to the accurate production of the movement. LTP, as seen from these studies, may play a major role in the production and retention of motor learning by altering synaptic connections between functionally related cortical areas.

In addition to LTP, other factors have been discovered that may play a role in cortical plasticity. Latent synaptic connections in motor cortex have been discovered and these may play a role in the rapid reorganization Nudo described in his studies [4]. Jacobs and Donaghue (1991) demonstrated that reductions in local inhibition can temporarily rearrange the relation between an area of M1 [129]. Jacobs and Donaghue proposed that organization of the cortical motor map may be regulated by GABA-mediated inhibitory local circuits. They speculate that inhibitory cells project to nearby pyramidal neurons and suppress the excitation from surrounding represention s. They further suggest that "small adjustments in intracortical inhibition would be sufficient to unmask latent connections, and reorganize the M1 map" (p. 945). Jacobs and Donaghue conclude by suggesting that changes in GABA activity may lead to temporary associations between adjacent cell groups, enabling reorganization. Along this line of inquiry, Ziemann, Hallett and Cohen (1998) investigated mechanisms of deafferentation-induced plasticity [130]. Using ischemic nerve block, CNS-active drugs (lorazepam, lamotrigine and dextromethorphan) and repetitive TMS, the investigators found the combination of CNS-active drugs in the presence of ischemic nerve block plus repetitive TMS produced plasticity in the human motor cortex as evidenced by increased motor evoked potentials. The authors concluded that "deafferentation induced increases in MEP size by rapid downregulation of GABA-related inhibitory circuits" (p. 7005). These mechanisms produced long-lasting reductions in inhibitory intracortical inhibition which may be related to LTP-like mechanisms given its duration and the involvement of NMDA receptor activation.

As noted, the changes in cortical plasticity documented in the animal studies of Nudo and human studies which utilized functional MRI are likely the result of synaptic reorganization involving LTP and alterations in intracortical inhibition. As an example, it may be that these mechanisms are responsible for the changes noted by Nudo et al. (1996), where following long-term practice, co-contracting muscles used in the task came to be represented together in motor cortex [93]. One could hypothesize that LTP produced and maintained the strengthening of the local neuronal connections and this connectivity was initially favored by changes in local intracortical inhibition.

Adaptation or reorganization of synaptic properties is phenotypically expressed as behavior. Functional imaging and neurophysiologic studies such as TMS allow the documentation of changes in cortical activation that are associated with behavior. There have been relatively few imaging studies of motor plasticity in normal subjects. Most imaging research has investigated the role of plasticity in subjects recovering from cortical injury. In the next section, the contemporary functional imaging literature will be reviewed in order to demonstrate that cortical reorganization is a real phenomenon in human subjects. Based on the prior discussion, it is important to remember that functional imaging displays changes that are three steps removed from the primary mechanisms responsible for cortical reorganization. The primary event is synaptic adaptation by LTP, intracortical inhibition, or other phenomena coupled with the summation of neuronal activation in the newly coherent neuronal population controlling the motor activity. The second event may be the stimulation of neuronal metabolism and the concomitant release of vaso-active substances that promote regional blood flow increases. The third event is the change in blood oxygenation that leads to the activation

maps seen in imaging studies. Regardless, recent imaging work has supported the findings that the brain is able to adapt to injury by altering its organization.

Lesion-Induced Plasticity: Imaging Studies

The observation that functional recovery is evident in many patients following cortical injury suggests that the brain has reorganized itself to adapt to the particular injury. The neuroanatomic and neurophysiological mechansims which support recovery have been investigated using neuroimaging and neurophysiology techniques. Chen et al. (1998) investigated the mechanisms of cortical reorganization following lower limb amputation using TMS [131]. TMS stimulation on the amputated side produced lower limb muscle activation at a lower threshold than on the normal side. Significantly less intracortical inhibition occurred on the amputated side and Chen et al. speculate this was related to reductions in GABAergic inhibition. Chen and his associates' findings support Jacobs and Donoghue (1991) who also demonstrated that reductions in local inhibition can temporarily rearrange an area of M1 [129]. In addition to identifying changes in reorganization using TMS, research into cortical reorganization has utilized other functional techniques such as PET and fMRI.

Chollet et al.(1991) studied the functional anatomy of motor recovery after middle cerebral artery stroke in humans using PET [132]. Regional cerebral blood flow was seen in the sensorimotor cortex ipsilateral to the lesion during ipsilateral paretic finger tapping. The onset of ipsilateral activation suggested that lateralized motor systems controlling movements in the normal fingers also participated in the recovery of movement in the initially paretic fingers. Chollet et al. again return to theory of decreased intracortical inhibition suggesting that the mechanism of recovery may be

provided by changes in synaptic efficiency or the use of "alternative conduction pathways." They conclude that synaptic input to ipsilateral sensorimotor cortex is increased due to decreased transcallosal inhibition. Seitz et al. (1998) evaluated the role of the premotor cortex in recovery from middle cerebral artery infarction using TMS and PET [133]. Studies conducted after stroke recovery noted bilateral increases in regional cerebral blood flow to the dorsolateral and medial premotor areas but no increases were noted in the sensorimotor cortex of either hemisphere. Seitz et al. suggest that the recovery was mediated by reorganization of "body map circuits" or by recruitment of non-primary motor "output modules" in either hemisphere. As discussed, the SMA cortex provides direct projections to spinal neurons and also gives rise to a portion of the corticoreticular spinal tract that is bilaterally organized. Seitz proposes that activation of SMA, premotor cortex, and prefrontal cortex reflected compensatory mechanisms that served to overcome the residual motor deficit. Rossini et al.(1998) combined both the temporal resolution of MEG and TMS with the spatial resolution of fMRI to perform a case study in a patient with a motor stroke [134]. All three methods demonstrated an asymmetrical enlargement and posterior shift of the sensorimotor areas in the damaged hemisphere. Specific anatomical landmarks were not mentioned.

Plasticity Summary

The goal of this project was to determine if cortical representations expand after a prolonged period of imagined motor practice. Based on the work of Karni and colleagues [5], we expect to find indirect evidence of cortical plasticity in the form of enlarged fMRI activation maps in areas that control hand movement. While recent

evidence has suggested that cortical representations expand after executed practice, the idea that the adult human brain can adapt to its environment is now provable by many new techniques. Modern techniques, such as intracellular and patch clamp recording, have allowed access to the cellular and subcellular mechanisms that drive neuronal activity, fostering the notion that neurons can adapt to stimuli and subsequently alter motor output. It seems clear that our ability to learn and recover from devastating injuries is based upon the ability of our neurons to undergo simple but dynamic changes both within the context of the cell and across associations with other neighboring cells. This review of the contemporary literature supports that idea that synaptic and cellular changes drive cortical reorganization, i.e., neuroplasticity. Thus, when evaluating functional imaging studies that show changes in cortical activation maps, it must be remembered that the changes seen on this macroscopic scale are in fact driven by cellular and subcelluar mechanisms. This project will concentrate on the macroscopic changes observed with functional imaging, but it must be remembered that our results are functionally several steps downstream from the actual functional reorganization and adaptation. Fortunately, neuronal activation and the subsequent changes in regional blood oxygenation occur quite rapidly. This allows functional imaging techniques to remain time-linked, highly sensitive and specific to the task supported by the underlying neurons.

Functional MRI

General Background

As technology has advanced in recent years, it has become possible to not only glimpse views of the structural components of the brain, but also to see how those components function in relation to different tasks. Functional imaging provides a unique opportunity to study how the brain operates in vivo. Prior to 1992, functional brain imaging was performed using techniques such as positron emission tomogaphy (PET) or single photon emission computed tomography (SPECT). These techniques provided the first opportunity to study the brain without breaching the cranium. As revolutionary as these techniques were, they still had severe limitations. Both techniques use ionizing radiation in the form of radionuclide tracers to produce an image. Secondly, the spatial resolution of these techniques is markedly worse than that obtainable with newer techniques such as functional MRI. The resolution with PET is typically on the order of 16 mm after Gaussian smoothing and SPECT studies generally report resolution in the 9-12 mm range [135]. Today's fMRI studies can obtain resolutions on the order of a few millimeters but, more importantly, fMRI uses no radiation so studies are safe and can be repeated multiple times.

Functional MRI is a relatively recent technique that began in 1990 when Ogawa et al. at AT&T Bell laboratories reported the first use of magnetic resonance imaging as a means of investigating changes in regional cerebral blood oxygenation that correlated with physiological perturbations [136]. Ogawa et al.described using an imaging

technique that took advantage of the magnetic properties of oxygenated and deoxygenated blood. Ogawa et al. named the imaging technique blood oxygen level dependent contrast or "BOLD" endogenous contrast. The authors noted that the physical mechanism underlying the BOLD response results from the fact that deoxyhemoglobin alters the local magnetic field in its vicinity, particularly when it is compartmentalized as within red blood cells and vasculature. The potential use of BOLD imaging was described as an adjunctive study to complement PET imaging; however, others in the field later provided evidence that fMRI can stand as an independent measure of brain functional activation.

Following the report in 1990 by Ogawa et al. that the BOLD imaging technique is altered by physiologic mechanisms, attempts proceeded to reproduce the findings in humans at lower field strengths. The first human task-induced functional MRI study was performed using gadolinium contrast (Gd-DTPA) by Belliveau et al. in 1991 with visual cortex stimulation [137]. Contrast-enhanced changes in local cerebral blood volume were noted following changes in the gradient echo EPI signal from vessels and the surrounding tissue areas. Following these studies, competition began to use the BOLD contrast technique, obviating the need for exogenous contrast agents. Three reports were subsequently published separately by Kwong & Belliveau , Ogawa and Ugurbil, and Bandettini et al. within five days of each other in 1992, demonstrating cortical activation using the BOLD technique [138-140]. Kwong and Belliveau (1992) publishing in the Proceedings of the National Academy of Sciences (PNAS) in June of 1992, demonstrated that subjects shown a 8-Hz patterned flashing photic stimulation, demonstrated increased primary visual cortex activation of 1.8% versus the resting state

at 1.5 tesla [139]. Similar changes were also noted in primary motor cortex during finger tapping experiments. Kwong and Belliveau conclude that "by using intrinsic blood-tissue contrast, functional MRI opens a spatial-temporal window onto individual brain physiology" (p. 5675). The following month Ogawa et al. (1992) also published in the PNAS results demonstrating that photic stimulation using an alternating red/green checkerboard produced intrinsic signal changes ranging from 5-20% of baseline activation at 4T [138]. Ogawa et al. concluded by suggesting " the amplitude, sign, and echo-time dependence of these intrinsic signal changes are consistent with the idea that neural activation increases regional cerebral blood flow and concomitantly increases venous oxygenation" (p. 5951). Bandettini et al.(1992) mirrored the prior results, demonstrating 4.3% signal changes in motor cortex following a simple finger tapping paradigm [140]. The implications of these early contributions are significant and have provided the foundation for many subsequent studies that take advantage of functional MRI's unique qualities including a) high spatial and temporal resolution and b) non-invasiveness and repeatability.

The physiologic mechanisms underlying the BOLD response are complex, but an understanding of this phenomenon is critical for interpretation of functional imaging studies. Kim and Ugurbil (1997) provide a comprehensive review of the mechanisms underlying the BOLD response [141]. The BOLD signal is produced because deoxyhemoglobin acts as an endogenous intravascular paramagnetic contrast agent. Deoxyhemoglobin causes changes in the local magnetic field which cause a detectable local distortion of the magnetic field surrounding red blood cells and the surrounding blood vessels. The local distortion affects the MR behavior of the water proton nuclei

within and surrounding the vessels, increasing susceptibility induced intravoxel dephasing. As a result, the transverse relaxation time T2 and the apparent transverse relaxation time T2* are decreased, with the decrease in T2 and T2* resulting in an attenuation of the MR signal intensity. The decreased signal is noted as a dark area on the resulting image.

Certain specific variables can influence the BOLD phenomena. Ogawa et al. (1990) noted that the size of the susceptibility-induced local field gradient depends on both the concentration of paramagnetic deoxyhemoglobin and the orientation of the vessel relative to the main magnetic field [136]. In addition, Ogawa et al. (1992) noted that part of the contribution to BOLD contrast comes from tissue water around the blood vessel and less from blood water itself and that the field distortion that produces the image extends to the area around the blood vessel at distances twice the radius of the vessel [138]. In addition to intrinsic tissue properties, the field strength of the imaging system contributes to the ratio of signal to noise. Ogawa et al. (1993) noted that the signal intensity changes observed at 4T were significantly large than those noted at 1.5T suggesting that a "superlinear" increase in fractional change occurs with field strength [142]. Since the technique's inception, functional MRI researchers have attempted to fully understand the mechanisms by which the signal attenuation occurs and at an even more fundamental level, research has been ongoing to understand the mechanisms by which neuronal activation and blood oxygenation are coupled.

Cerebrovascular Physiology and Autoregulation

It is well known that neuronal activation changes the ratio of deoxygenated and oxygenated blood due to cerebrovascular autoregulatory mechanisms; however, the

exact mechanisms by which these changes occur are unclear. Pauling and Coryell were the first to demonstrate that deoxyhemoglobin is paramagnetic and that the magnetic property of blood depends on the degree of blood oxygenation and therefore on physiology [143]. The effects of deoxyhemoglobin on MRI signal increase as the concentration of deoxyhemoglobin increases. As more deoxyhemoglobin is introduced into the local environment, susceptibility induced intravoxel dephasing increases, leading to decreased T2 and T2* relaxation times. Ogawa et al. (1992) suggested that the T2* changes were caused by a stimulus-induced change in magnetic suscepatabilty that resulted from a "reduced concentration of the paramagnetic species deoxyhemoglobin in venous blood" (p. 5954) [138]. This suggestion that oxygen concentration in the venous system actually increases with neuronal activity has been the focus of much research and debate since this concept was introduced.

Roy and Sherrington (1890) first proposed that the brain "possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations in functional activity" (p. 88) [144]. As noted, functional imaging studies take advantage of this principle by evaluating the regional changes in deoxyhemoglobin concentration to produce images of cortical activation. The changes in deoxyhemoglobin concentration occur due to autoregulation of local blood flow, presumably in response to neuronal activation. Grinvald et al. (1991) using near infrared spectroscopy noted a repeatable pattern of blood oxygenation changes following the initiation of various tasks in monkey visual cortex [145]. Grinvald et al. modeled the physiology behind the blood oxygenation changes as follows: first, a task initially causes a rapid consumption of oxygen while cerebral blood flow (CBF) lags

behind. Secondly, there are simultaneous increases in deoxyhemoglobin that peak after 2.5 sec that should theoretically result in a brief negative BOLD signal. Subsequently there is an increase in CBF and oxygen delivery that exceeds the tissue oxygen extraction resulting in an increase in the signal intensity of T2* and T2-weighted images. The change in T2* or T2-weighted images forms the basis for functional image analysis. Because functional MRI is a step removed from the actual process of neuronal metabolism, it is important to discuss the mechanisms of cerebral autoregulation, since this mechanism is the ultimate effector of the BOLD signal used to generate fMRI images.

Maintenance of cerebral blood flow is thought to be the most important task for the cardiovascular system in humans. In contrast to other regions of the body, the total blood flow to the brain remains relatively constant under a wide variety of conditions. Despite the constancy of total flow, regional flow changes markedly, paralleling changes in regional cerebral activity. The brain receives approximately 12-15% of resting cardiac output and total cerebral oxygen consumption accounts for 15-20 % of the basal metabolic rate. It was originally thought that because the brain sits in the rigid cranium, total cerebral blood volume is constant and because of this cerebral blood flow could not change. It is now well known that chemical and/or metabolic changes result in alterations of regional and total cerebral blood flow likely due to influences exerted on local vasculature. Reina-De La Torre, Rodriguez-Baeza, and Sahuquillo-Barris (1998) used scanning electron microscopy to evaluate the morphological characteristics and distribution of human cortex arterial vessels [146]. By evaluating the angioarchitectonic pattern and the anatomical structures the authors confirm that blood

flow autoregulation likely occurs at the arteriolar and capillary level. Autoregulation at the arteriolar level is likely mediated by smooth muscle cells and "sphincter-like structures" through the myoendothelial junctions. Cortical capillary vessels may also play a role in autoregulation due to their frequent anastomoses and by the action of endothelial cells and pericytes. Reina-De La Torre et al. conclude that the "arteriolar and capillary networks and their indigenous cell types seem the likely target of substances that provide for neurovascular autoregulation" (p. 94).

Estrada and DeFelipe (1998) discuss two different hypotheses that have been used to explain the local regulation of cerebral blood flow [147]. The first hypothesis proposed is the metabolic hypothesis, which states that neuronal activation and the subsequent increase in metabolic activity result in the release of certain products, including carbon dioxide, potassium, and adenosine, which have relaxant properties on vascular smooth muscle with the result being increased regional cerebral blood flow. The second hypothesis is the neurogenic hypothesis, which states the microvessels in the neocortex are innervated by intrinsic neurons containing neurovascular neurotransmitters. The neurons would be activated concomitantly with their neighbors causing increased regional blood flow.

Brian, Faraci, and Heistad (1996) provide a comprehensive review of the chemical and cellular mechanisms implicated in the regulation of the cerebral circulation [148]. The roles of several vasodilator substances are discussed, including nitric oxide (NO), trigeminal peptides, and potassium channels, and the vasoconstrictor action of endothelin is reviewed. A summary of the findings in this review follows. Nitric oxide is a potent dilator of cerebral vessels and approximately 2% of

parenchymal neurons normally express the brain isoform of NO-synthase [149]. NO is highly diffusible and the presence of NO-synthase in parenchymal neurons that lie near blood vessels suggest NO produced during neuronal activation could influence local cerebral blood flow. Activation of perivascular neurons may cause NO-mediated dilation of vessels. Astrocytes also express low levels of NO-synthase and produce NO in response to receptor-mediated stimuli. The close proximity of astrocyte foot processes to cerebral vessels suggest that NO elaborated from these structures could influence vascular tone. NO is implicated as a mediator of several processes, including vasodilation during hypercapnia, coupling of metabolism and blood flow, cortical spreading depression and vasodilation in response to excitatory amino acids [150, 151]. The most relevant to functional MRI imaging is that nitric oxide is implicated as a mediator in blood flow and metabolism coupling. Activation of glutamate receptors with NMDA or kainate leads to NO-mediated dilation of cerebral arterioles. Stimulation of both cerebellum and sciatic nerve has been shown to produce local vasodilation in the cerebellum and somatosensory cortex, respectively. Although NO is an important mediator, inhibition of NO synthesis only partially abolishes the vascular responses, indicating that other mechanisms are likely involved in autoregulation [147].

Another compound implicated in autoregulation is the trigeminal peptide, calcitonin gene-related peptide (CGRP), which is contained in cerebral perivascular sensory nerves arising primarily from the ipsilateral trigeminal ganglia. Cerebral vasodilation during hypotension appears to be mediated by the release of CGRP [152]. CGRP may contribute to cerebral vasodilation during a variety of processes, including

autoregulation during hypotension, cortical spreading depression, seizures, and endotoxin exposure [153, 154].

Endothelin is another compound implicated in autoregulation. It has three isoforms, two of which are produced in the brain. Binding sites for endothelin are located throughout the brain on astrocytes and neurons [155]. In vivo application of endothelin produces dilation of cerebral vessels; however, the effects on vascular autoregulation are unclear. Endothelin has been implicated as a mediator in cerebral vasospasm following subarachnoid hemorrage [156].

Adenosine is another compound implicated in cerebral autoregulation. Shin, Shin, and Hong (2000) investigated the role of adenosine A(2B) receptors in vasodilation of rat pial artery and cerebral blood flow autoregulation [157]. Results suggested that adenosine-induced vasodilation via activation of A(2B)-adenosine receptors of the rat pial artery was coupled to the production of nitric oxide, which they suggest contributes little to CBF autoregulation. While adenosine has been repeatedly implicated in autoregulation, the exact mechanism by which it acts remains unclear.

Carbon dioxide is the most basic player in cerebrovascular autoregulation. Increasing levels of carbon dioxide result in cerebral vasodilation, while decreasing concentrations of carbon dioxide produce cerebrovascular constriction. Madden (1993) reviewed the effect of carbon dioxide on cerebral arteries [158], concluding that "there appear to be complex interactions between the effect of extracellular pH on the calcium influx and potassium permeability possibly coupled with an influence of intracellular pH on the mobilization of free cytosolic calcium. In the normal subject, changes in both intra/extracellular pH are effectively buffered so the cerebrovascular tone and

cerebral blood flow eventually return to normal levels" (p. 233). Importantly, Madden also notes that the responses of the cerebral vessels to carbon dioxide are "not constant or fixed", varying with oxygen concentration, blood pressure and age.

It is clear that cerebral autoregulation is affected by many endogenous and exogenous factors. The exact mechanisms controlling autoregulation are still not completely understood and this has led to more debate regarding whether the effects of neuronal metabolism are directly coupled with increases in regional cerebral blood flow. Coupling refers to a one-to-one association of blood inflow and oxygen extraction, i.e., every milliliter of blood delivers x-quantity of oxygen that is completely extracted by the tissue. The issue of coupling between cerebral blood flow and metabolism is not a new debate and questions about this topic pre-date the introduction of fMRI.

Early work by PET researchers including, Fox and Raichle, demonstrated an uncoupled response between neuronal activation/ oxygen consumption and regional cerebral blood flow [159]. As an example, Fox and Raichle (1988), demonstrated that somatosensory activation increases regional cerebral blood flow and cerebral glucose metabolism by 30-50% while the oxygen metabolic rate increased only 5% [160]. This results in the net oxygen extraction being decreased. These concepts play an important role in the interpretation of fMRI studies since the signal that is ultimately interpreted is based on the proportion or concentration of local deoxyhemoglobin. A recent study attempted to use MRI to look at changes in oxidative metabolism during changes in cellular activity. Davis et al. (1998) compared the BOLD signal and perfusion-sensitive MRI using carbon dioxide breathing as a physiological reference [161].

Results demonstrated that during task performance oxygen consumption increased 16% while blood flow increased 45%. These results support the uncoupling hypothesis of blood flow vs. oxygen extraction. Others, however, have proposed models that show cerebral blood flow is coupled to oxygen metabolism. The coupled hypothesis states that flow increases by an amount equivalent to the necessary increase in the rate of delivery of oxygen to the tissue. Kida, Yamamoto, and Tamura (1996) used near infrared spectrophotometry and MR in the rat to demonstrate that the apparent transverse relaxation time between two conditions was linearly correlated with the deoxyhemoglobin concentration [162]. Buxton and Frank (1997) also advocate a model for the coupling of cerebral blood flow and oxygen metabolism during neural stimulation [163]. The authors note that the rate of delivery of oxygen to tissue will increase much more slowly than the increase in flow because the net oxygen extraction fraction decreases with increasing flow. This means that the disproportionately large changes in CBF compared with oxygen metabolic rate found during neural stimulation are consistent with the tight coupling of flow and oxygen metabolism. These hypotheses contradict the earlier work of Fox and colleagues and others who support the uncoupled hypothesis.

Currently the issue of whether oxygen metabolism is coupled or uncoupled with blood flow remains a controversial topic with important implications for the interpretation of functional MRI studies. Regardless of the exact mechanism, we do know that after a short period of neuronal activation, the levels of deoxyhemoglobin first decrease and then increase. This information is useful in producing functional activation maps.

Functional MRI Task Design and Technical Considerations

Functional MRI tasks are designed to take advantage of the cyclical fluctuation in regional blood oxygenation and flow that occurs during task performance. By comparing the MRI signal generated as a result of the flux in deoxyhemoglobin and oxyhemoglobin concentrations in the local environment, maps of regional neuronal activation can be generated. When discussing activation maps it is important to remember that what is being imaged is blood-flow-related changes and not direct neuronal activity. Nadeau and Crosson (1995) comment on this limitation, discussing the concept of the "Peter Principle" [135]. The authors noted that activation of neurons with distant projections may cause activation to be noted in the neurons receiving the projections with little change occurring in the neurons that elicited the activation. It is suggested that "increased synaptic activity may have a tendency to extend one level beyond the regions principally engaged in a function, within the hierarchy of neuronal networks relevant to that function" (p. 145). Another limitation of functional imaging that should be considered when interpreting imaging studies is the idea that both excitatory and inhibitory neuronal activation increase neuron metabolism. It is an important concept that should be considered so that excitatory and inhibitory mechanisms of cerebral control are addressed in each study. In light of the analytical problems associated with functional imaging, a wealth of information can be obtained through the implementation of relatively simple task paradigms. To extract this information, a host of new strategies for fMRI signal processing and data analysis have been proposed.

Following the use of subtraction techniques in the early 1990's, researchers began to understand that large vessel artifacts and motion-induced activation were accentuated by the image subtraction technique. New data analysis techniques were introduced to reduce the production of false positive pixels. One common second generation data analysis technique employs a blocked design paradigm for the performance and subsequent analysis of fMRI data. The rationale for using a blocked design came about after investigators looked at the temporal course of the hemodynamic response [164]. A typical paradigm uses a box car function as an "idealized" reference wave which is correlated to the periodic fluctuation in signal intensity seen as the hemodynamic response occurs in response to neuronal activation. Typically, the design incorporates alternating periods of task performance with rest periods where the subject remains motionless attempting not to perform any task-related functions. Waveforms are typically staggered or phase-shifted so as to address the temporal evolution of the signal changes; however, the temporal component is typically not considered in the interpretation, only the spatial location of the activity is retained.

The complex process of creating a final fMRI map is a multi-step endeavor that is fraught with assumptions and statistical manipulations; however, the final product has been shown to be highly representative of the underlying neuronal population that subserves the task performed [84]. This fidelity is obtained by using many techniques in the post-processing and data analysis portions of the experiment. There are many first order alterations in the acquired fMRI signal that result from variables such as head motion, physiologic artifacts, scanner magnetic inhomogeneity, and other issues. These

must be accounted for during pre-scanning and post-processing sessions to alleviate sources of false activation.

First, gross head motion has been a major problem faced by fMRI researchers since the first imaging trials began [135]. Head motion not only causes misregistration of structural and functional datasets, but it also can independently cause false activation of pixels if the head movement is synchronized to the task performance [165]. To limit head motion researchers have both head immobilization and post imaging methods to counteract motion artifacts. Head stabilization devices included a hockey-style mask, a vacuum fixation device, surgical tape, foam pads, and bite bars. Post-processing strategies to correct motion artifacts have included in-plane image registration using intensity based registration, contour based registration techniques or viewing of cine-loops of serial slices to determine if head motion occurred [166, 167]. Another source of signal error comes from linear signal drifts. Signal drifts are noted in most MRI scanners and are due to slight inhomogeneity of the static scanner field. Linear drifts are removed as part of most imaging analysis packages. Finally, aberrant pixels, defined as pixels with very large, non-physiologic percent signal change, are often discarded in an attempt to limit both motion-induced activation and the contribution of large vessels to false activation. Once these initial data corrections are performed the analysis of pixel time course series characteristics is performed.

As noted, the initial method for data analysis was the subtraction method; however, it was found to be unsatisfactory because a threshold could not be assigned to determine which pixels were "activated" and this often resulted in false positive activation associated with large vessels [168]. Because of this limitation, other

statistical methods were employed for fMRI data analysis including t-tests, cross correlations, and third generation analysis techniques such as principal component analysis or fuzzy cluster analysis. As with any statistical test, a significance value must be assumed. The difficulty is in assigning a significance level that includes the majority of the pixels with "true positive" activation and discarding those with "false positive" activation. Kim and Ugurbil (1997) note that "although the percent signal changes are dependent on slice thickness, resolution, echo time, etc., the average signal change in the volume of interest can provide insight into the origin of activation" (p. 230) [141]. It is useful to briefly discuss the two most common methods of fMRI data analysis: Student's t-test and the cross-correlation method.

The use of a parametrical Students' t-test is one of the most common methods of calculating fMRI maps. Comparison of the ratio of signal difference of the means in two conditions (active vs. rest) to the standard error of the difference of the means produces a significance value (P). When one assigns a standard P-value of 0.05 that means that five in 100 pixels are significant or "active" by chance alone. This is unacceptable since most imaging studies have thousands of pixels so a modified Bonferrroni correction is applied to reduce the P value to exclude more random pixels. The Student's t-test is an effective analytical tool; however, it ignores the time dependency of the signal intensity which could be used as an additional factor in data analysis.

Cross correlation coefficients are calculated between the time course of the pixel intensity and a reference waveform which is based upon the task performed. Bandettini et al. (1993) provide an excellent description of the time course series,

describing the plot of signal intensity versus time as a "temporal-spatial" plot [164]. Examination of the time course data for an individual pixel across an experiment shows the MRI signal fluctuates from baseline values to a heightened signal response following induction of task performance. The signal intensity plateaus during the task and finally returns to baseline following termination of task performance. The process is repeated to generate the cyclical temporal-spatial plots. The final statistical maps generated using a cross correlation technique are based on the correlation of the idealized reference waveform to the actual sinusoidal fluctuation in signal generated during task performance.

Recent Technical Advances in Functional MRI

The Student's t-test and cross correlation technique assume an a priori knowledge of brain function, at least in regard to the temporal responses of the different brain regions analyzed. Additional analysis methods are being developed to remove the need for a priori assumptions regarding the data. Fuzzy cluster analysis and principal component analysis are two such methods. Fuzzy cluster analysis partitions data into representative subgroups or clusters to separate relevant information from noise or artifacts. Fuzzy clustering uses a membership function as a similarity index [169]. In principal component analysis many components exist above the random noise level of the scan, including both task induced activation and movement-induced artifacts. By separating the task vs. movement activation reliable fMRI maps can be obtained. In addition to these data analysis techniques, newer methods have been developed for fMRI data acquisition.

Event-related fMRI is a new technique that attempts to utilize the high temporal resolution possible during fMRI scanning [170, 171]. Single tasks are performed instead of multiple repetitions of single tasks, with data analysis occurring on single events instead of on blocks. The neuronal response to a single task provides enough change in signal intensity to create useful fMRI images. By performing selective averaging, the same data can be extracted from single event trials as is seen during box-car designs. Event-related fMRI will prove useful for tasks where intermixed trials are performed. The most useful benefit may be the ability to resolve temporal changes occurring across the brain during cognitive tasks.

Functional MRI is in its infancy and promises to become the most important human neuroscience tool of the new century. With that said, fMRI has many complex pitfalls that must be addressed before a study should be considered of adequate quality to make experimental conclusions. Issues such as image acquisition and data post processing weigh heavily on the integrity of an fMRI research study. The experimental design is among the most critical factors limiting experiment success; new task paradigms hold the promise of advancing our understand of brain function and disease. Finally, the basic physiological properties that underlie the BOLD response need to be determined and with those advances will come the possibilities of manipulating the fundamental variables that create the BOLD signal. Functional MRI has the potential to explain many complex human brain functions and behaviors; however, technology is no substitute for good scientific reasoning and sound experimental design.

CHAPTER 3
METHODOLOGY

Overview, Rationale, and Experiment Hypothesis

The human brain is a complex, dynamic organ capable of adaptation to environmental stimuli. Animal research and recent functional imaging experiments have demonstrated that the human cerebral cortex changes with motor practice by increasing the cortical representation devoted to the particular practiced task, a concept termed neuroplasticity. fMRI studies have demonstrated motor cortex activation occurs when subjects imagine executing movement. While functional imaging has demonstrated increased cortical activation (changing cortical representations) with motor practice, no studies have evaluated the effect of imagined motor practice on cortical activation/representations. The purpose of this research is to investigate whether imagined practice of a simple motor sequence causes the cortical representations to expand in a similar fashion to that seen with actual execution of a motor sequence. This line of questioning would have broad implications in neurorehabilitation and sports psychology.

Based upon the aforementioned studies and rationale, the following questions and predictions were investigated:

1) Is there a quantitative difference between the activation seen during executed vs. imagined motor practice? Imagined motor practice was hypothesized to

enlarge cortical representations but to a lesser degree than actual executed motor practice.

2) Is there a quantitative difference between the activation seen during the experimental (practiced sequence) and the control (random sequence) task? Both the imagined and executed practice groups were hypothesized to show an increase in cortical representation during tapping of the practiced sequence with the executed group having a larger response. Additionally, the increase in cortical representation was expected to be specific for the practiced sequence thus the control task (random sequence) should not demonstrate an increase in cortical representation.

3) Are changes seen with functional imaging correlated with changes observed on behavioral tests of manual dexterity (finger tapping speed and accuracy, both before & after practice)? Both imagined and executed practice were hypothesized to lead to behavior improvements in both tapping speed and accuracy; however, executed motor practice was expected produce a more robust improvement compared to imagery. These changes were expected to correlate with the enlargement in cortical representations that occur as the result of practice.

Subjects and Exclusion Criteria

Twenty-five medical students from the University of Florida, age 18-40 were enrolled in the study. All were strongly right hand dominant as assessed by the Waterloo handedness survey [172]. Gender was evenly distributed among the groups. Only non-smoking subjects were recruited since carbon monoxide is a smoking by-

product and can reduce the oxygen carrying capacity of hemoglobin. Subjects were randomized to one of two groups:

Executed: Executed movement during practice session

Imagined: Imagined motor movement during practice session

Exclusion criteria included the following: 1)MRI incompatibility (implanted medical devices, cardiac pacing units, corneal transplants, orthopedic hardware near the head, shrapnel, extensive fixed dental appliances, claustrophobia), 2) left handedness or mixed dominance, 3) excessive pain in any joint that would limit participation or movement disorders, 4) serious uncontrolled medical problems assessed by routine history and physical exam, 5) history of progressive neurological disease, head trauma or loss of consciousness, 6) prior neurological surgery, and 7) lack of availability for follow up testing.

Behavioral and Performance Testing

Human subjects have tremendous variability in their dexterity on simple movement tasks such as finger tapping. Variability also exists in the degree of hand dominance, even in subjects who consider themselves strongly right hand dominant. To ascertain the degree of right hand dominance and to determine the level of motor dexterity for each subject in the null condition, both written and performance testing were employed. Two written surveys were used to ascertain the degree of handedness laterality and the innate hand motor skills present at the beginning of the study. The written surveys included

1) Waterloo Handedness Inventory [172]—A highly reliable measure used to calculate handedness laterality scores. These scores were used to exclude

subjects who were not strongly right hand dominant. Right hand dominance was defined as subjects with scores of 87.5 or higher.

2) A dexterity survey-- (the survey, developed for this study, asked questions about skills requiring manual dexterity such as typing, sewing, or other manual tasks involving skilled use of the hands).

Written surveys were taken to obtain background that might later help to explain variability in the performance data; however, physical tests of motor dexterity were used as the primary objective rating of initial motor performance versus post-practice improvements. The performance testing was conducted as follows: Subjects were naïve to the experiment when they reported to the MRI center. Prior to scanning, the subjects sat in a chair and rested their right forearm on their leg. A video camera was focused on the subject's right hand. Subjects were shown a finger tapping sequence written on a piece of paper and instructed to perform the task as rapidly but accurately as possible. Accuracy was stressed over the speed component of task performance. Subjects were also told not to look at their hand while performing the task. Given these directives, subjects performed four separate one-minute trials consisting of three unique finger tapping sequences, the "practiced sequence", which was the sequence practiced at home, was repeated twice in succession followed by two random sequences which were not practiced. A ten second break occurred between trial runs. The movement order for the finger tapping sequences were as follows: the "practiced" sequence was thumb to finger 5, 2, 4, 3 and repeat; the "random" sequence used in the first one minute random test was thumb to finger 2, 4, 5 ,3 and repeat; and finally the 'random" sequence used in the second one minute random test was thumb to 4, 5, 3, 2 and repeat.

After subjects returned from three weeks of practice, either having been randomized to the executed or imagined groups (both of which rehearsed the "practiced" sequence), the same videotaped practice session was repeated having the subjects perform the "practiced" sequences twice followed by the two "random" sequences.

Videos of motor performance both before and after three weeks of practice (executed or imagined) were evaluated for the following characteristics: 1) speed-raters counted the number of completed sequences tapped in 60 seconds. A completed sequence represented four finger taps conducted in the designated order. A completed error resulted in the sequence being discarded if the subject did not resume the correct sequence order, i.e., if a mistake in tapping was made, subjects who resumed the correct tapping order from the point before the error occurred were credited for a completed sequence. If a sequence was not performed to completion, i.e., four finger taps performed in the proper sequence, the taping was not counted as completed. 2) accuracy—raters counted both the number of completed and corrected errors. Completed errors were defined as mis-ordered taps or tapping two or more fingers to the thumb simultaneously. Corrected errors were defined as incorrect movements, not hesitations, which were corrected prior to touching the fingers together. Samuel Browd rated the videotaped sessions unblinded. Five subjects were reanalyzed demonstrating a 96% intra-rater reliability.

An accuracy index score was developed for this study that heavily penalized subject errors committed during performance testing. The index was used not only to indicate improvements in speed, but more importantly, to take into consideration improvements in accuracy which were considered markers for task learning. The

accuracy index was defined by the following formula: Accuracy Index = (# completed tapping sequences ÷ (completed errors) + (corrected errors ÷ 2)). Videotaped motor performance served as an objective marker for improvement in motor performance. The results of videotaped motor performance were also correlated with changes in cluster size after the three-week practice interval.

Task Implementation during fMRI Studies and Home Practice

Functional imaging studies were used to ascertain the extent of activation in motor cortex. To determine the effects of practice versus non-practiced finger tapping, three different finger tapping tasks were developed. All tapping sequences were performed with the dominant right hand only. Each respective sequence was repeated throughout each functional imaging run during the "active" condition and each run was repeated three times for a total of nine functional imaging runs. The three tapping sequences that were imaged included:

1) "Sequential" Thumb (T) to 2,3,4,5,2,3,4,5 ⇒ repeat

2) "Practiced" Thumb (T) to 5,2,4,3,5,2,4,3 ⇒ repeat

3) "Random" random sequences during each "on" period

Description of Sequences Used During fMRI Scanning

"Sequential": "standard" finger tapping design. Serial tapping was performed from the second through fifth finger and repeated during the course of the fMRI trial. This sequence was used in the first experiment to establish the normative range for dominant, right hand motor cortex activation and to conduct test-retest reliability on activation maps.

"Practiced": The practiced sequence was the tapping sequence that was given to both the executed and imagined groups for practice at home for three weeks. During the first scanning session, subjects were not told this specific sequence was for them to practice at home nor were subjects aware that the practiced sequence would be repeated three times during the scanning session.

"Random": The random sequences consisted of sequential tapping paradigms that were novel and not repeated at any time during the scanning session. The subject performed a new sequence during each active phase of the fMRI acquisition. No two sequences were alike for the third experiment so practice effects were negated.

Home Rehearsal of the "Practiced" Sequence

After the first scanning session, each subject was given the "practiced" sequence to rehearse for three weeks. Subjects randomized to executed practice were instructed to rehearse the "practiced" sequence only with the right hand for 15 minutes per day. They were instructed to practice the task in a quiet environment, with a timer (provided), and with the hand resting on a pillow or flat surface. The practice tapping was to be done as rapidly as possible without making ordering mistakes. No other

explicit instructions were given regarding self-pacing or other practice parameters. Practice consisted of tapping the designated sequence using controlled, light touch of the finger pad to the thumb pad, without looking at the hand.

Subjects randomized to the imagined practice group also performed the "practiced" sequence; however, they did not execute the movement but instead imagined performing the task. Instructions were given to the subjects to perform the imagined movements from the first person perspective. They were told to perform the task using the same instructions given to the executed group, except they were to imagine themselves tapping the sequence without actually causing finger movement. The imagined group was told explicitly to "imagine what it feels like to touch each finger as you go through the series".

All subjects were given a sheet with the "practiced" sequence for use as a reference and a log-sheet that was to be filled out each day to document the time spent practicing the sequence. The form also included the location of practice and whether any factor in the day might have impacted the practice session, e.g., did the subject have any alcoholic beverages before practicing the sequence. To further compliance, telephone surveys were conducted weekly during the three-week practice interval to ensure subject compliance. Subjects were simply asked if they were executing the sequence or imagining the task. No formal questions regarding strategies or self-reported improvements were sought until the follow-up scan session debriefing.

Functional MRI Scanning Session Protocol

Subject Positioning and Task Presentation

Subjects were screened using the appropriate consent forms prior to being admitted to the scanning chamber. Once supine a "lifevest" head stabilization vacuum fixation bag was used for head restraint (materials: S&S X-Ray Company, Brooklyn, NY). The lifevest vacuum fixation bag is a clear, polyurethane bag filled with foam beads. Suction is applied to the outlet of the bag and as the air evacuates, the foam beads approximate, forming a semi-rigid mold of whatever solid object it surrounds. The device was based on a standard square vacuum fixation bag; however, the shape of the device was altered to provide subject restraint along the brow, under the chin, and along the sides of the head. These restraint points were chosen to reduce both in-plane and out-of-plane motion that can corrupt functional MRI scans. The device is currently under patent application. After patient positioning in the device, foam inserts were placed between the device and the head coil to provide further stabilization. Subject's hands were supinated and placed on their legs for visualization during tapping experiments. Blankets and body padding were provided as requested by the subject. Ear plugs were also provided to each subject.

Subjects were instructed to perform the finger tapping sequences as rapidly and as accurately as possible while remaining motionless in the scanner. The sequences were performed with the dominant, right hand only. Each sequence (sequential, practiced, and random) was repeated three times for intra-session averaging and determination if habituation or facilitation of repeated runs occurred. During the actual scanning session subjects performed the task when a signaling light was turned "on"

and remained at rest when the light was turned "off". Subject compliance and accuracy was assessed by evaluation of videotape taken in the scanner room during task performance.

Task cues were presented using one of the following methods: cardboard cue cards with the sequence written in large lettering, back-projection of an image of the sequence using MS Powerpoint (Microsoft Corporation, Seattle, WA), or by back-projecting the sequence using 35mm slides. Technical limitations initially prevented the use of the back-projected computer and 35mm slide images. The sequential and practiced sequences were repeated throughout the acquisition period so only one cue card or image was placed/projected continuously during the scanning session. The random sequence cues were changed at the beginning of each "activation" period. In addition to videotaping each session, an attendant (undergraduate assistant, Mr. Latimer) was in the scanner room to coach the subject and ensure task compliance. Figures 3-1, 3-2, and 3-3 schematically depict the tapping sequences performed during the fMRI trials.

Upon completion of each session, subjects were debriefed to assess compliance and task performance strategies. Subjects were unaware this inquiry would follow the conclusion of the imaging session. Murphy (1990) used a post-experimental interview to monitor subject's imagery experiences ensuring that subjects were able to comply with the experimental treatments [173]. This reportedly improved experimental control.

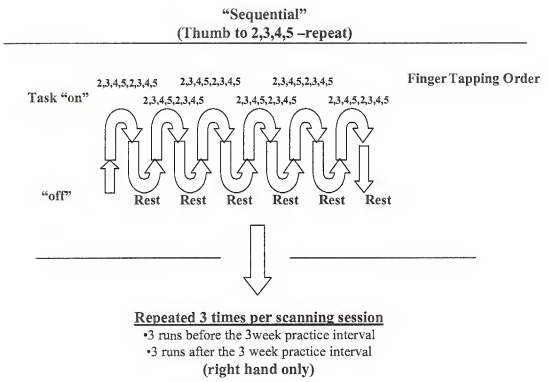


Figure 3-1. Executed vs. Imagined Motor Practice---fMRI Schema: The "Sequential" Sequence.

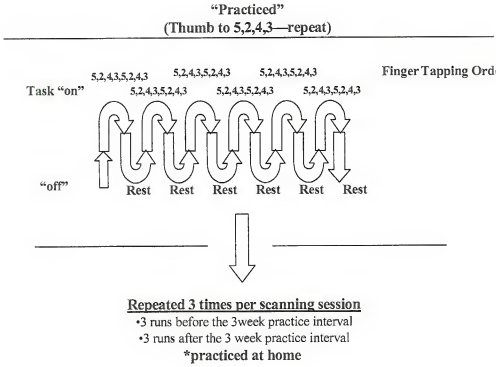


Figure 3-2. Executed vs. Imagined Motor Practice---fMRI Schema: The "Practiced" Sequence.

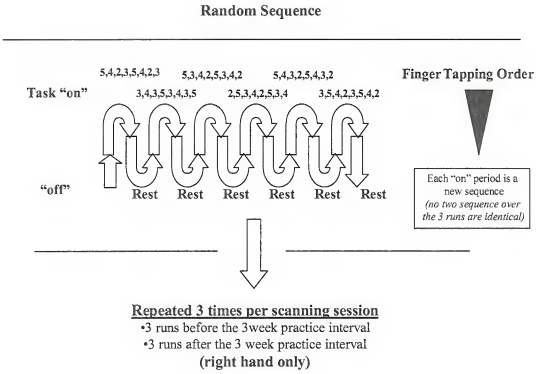


Figure 3-3. Executed vs. Imagined Motor Practice---fMRI Schema: The "Random" Sequence.

Image Acquisition Protocol

Functional, structural, and angiographic images were obtained on a GE 1.5T Signa scanner. A series of T1-weighted sagittal scout scans were acquired in order to determine the location of functional images. Head alignment in the coil was adjusted, if necessary, to center the images to within two degrees of the midline vertical. Nine axial functional images were obtained from the vertex down in 6.9mm thick gapless interleaved sections. Prior to acquisition of functional images, a time-of-flight MR angiogram (TE=6.6 ms; TR=40ms; FA=60 degrees; FOV= 18 cm; Matrix =128 x 128 mm) was obtained using the same nine slices used for functional imaging. This allowed functional imaging maps to be overlaid on MR angiogram slices to ascertain the existence of large vessel artifacts. For functional scans, a series of 64 images were acquired for each of the 9 axial slices using a spiral scan technique [174, 175] and a gradient echo pulse sequence (TE= 40 ms; TR= 870 ms; FA=45 degrees; FOV=18 cm; Matrix= 128 x128 cm; 4 spirals). Subsequent to functional imaging runs, a 3D structural imaging series was obtained using a T1-weighted spoiled grass sequence (TE= 7ms; TR=27ms; NEX=1; FOV=24cm; Matrix=256 x192; slices=124; thickness=1.3 mm).

Post-Processing and Image Analysis

Images were analyzed using AFNI software acquired from the Medical College of Wisconsin [176]. A program developed in our laboratory by Eddie Auerbach called Normalize Functional Datasets was used to exclude voxels where amplitude of signal change was above a preset criterion. A five percent cut-off was used in this study to exclude pixels that were outside the normal range associated with physiologic change;

examples would include pixels activated by head motion or large vessel artifact. Images from each imaging run were spatially registered in-plane to reduce the effects of head motion. Each image was aligned to a base image. The last image of the last functional imaging run was selected as the base image for each slice because acquisition of this image immediately preceded acquisition of the spoiled GRASS anatomic images on which functional images are overlaid. An iterative linear least squares approach was used for the pairwise registration procedure [177]. Prior to analysis, time series were examined for artifact caused by residual motion not corrected by this procedure by examining image slices in rapid succession. Visual inspection using this technique is capable of detecting movement on the order of approximately 1mm.

Another quality control measure was then instituted where a histogram of the percentage change of all voxels was created. All voxels in which the SD of variance exceeded 5% of the mean signal were set to zero in order to minimize large vessel effects or other sources of extraneous variation. Using AFNI, the time series (64 images) within each voxel of functional scans was correlated with an ideal, sinusoidal reference waveform. The ideal waveform was time locked to the alternating periods of rest and task performance. Nine phase-shifted waveforms were used to compensate for the temporal offset between spirals and slices during acquisitions, and the waveform generating the highest correlation with the acquired time series was used for each voxel. The resulting functional images for each task used the product moment correlation as the functional intensity. Each functional image was then overlaid on its corresponding 2D anatomic image. Voxels in which the product moment correlation between the acquired time series and the reference waveforms was 0.50 or greater were accepted as

indicative of functional activity. A more stringent analysis was also performed using 0.70 as the accepted cutoff for data inclusion. All post-processing steps and data analysis were performed on a Silicon Graphics Octane workstation at the University of Florida Brain Institute computer laboratory.

Region of Interest Analysis

Data was acquired in the axial plane and activation was assessed within six regions of interest (ROI): left and right precentral sulcus, left and right central sulcus and the left and right post-central sulcus. These areas were chosen to represent the premotor area, the primary motor cortex for the hand, and the somatosensory cortex, respectively. To isolate the ROIs a location of functional activity (LOFA) software program developed by Didem Gokay and colleagues at the University of Florida was used to locate activity with these regions of interest [178]. Because the anatomic and functional data were acquired with different sized matrices, LOFA required interpolation of both the anatomic and functional data sets to 2mm X 2mm X 2mm cubic voxels. The interpolation was accomplished by first making copies of the datasets, including the functional and 3D anatomic images. Next, features within AFNI allowed selection of the copied anatomic and functional images after which linear interpolation dimensions were selected and executed on the 3D anatomic image and all functional datasets. Once this step was accomplished, Samuel Browd used the LOFA software to define structural landmarks and quantify the volume of functional activation in specific ROIs. Using a mouse driven cursor, the operator was able to draw within the boundaries of the desired anatomical landmarks. The activity in the six regions of interest were evaluated and compared based on activation cluster volume.

Contiguous cluster volumes residing within the pre-central, central and post-central sulci were examined. These areas represented the likely location for activation associated with premotor, primary motor and somatosensory activation, respectively. Regions of interest were determined based upon anatomic features evident on the axial slices. All slices were 2mm thick after the prior interpolation procedure. The precentral sulcus was measured on slices moving from the inferior to superior direction. The location of the precentral sulcus was first evident parasagittally and it moved laterally on axial MR images when moving superiorly toward the vertex. The precentral sulcus was evident on approximately twelve slices which were measured from medial to lateral attempting to retain a nearly coronal plane. This avoided errors associated with tracing the superior frontal sulcus which on occasion merged with the precentral sulcus in a tangential fashion. The central sulcus was measured on ten slices. We used the inferior aspect of the hand-bump, a common radiographic feature that localizes the hand homunculus, to begin measuring the central sulcus. A conformal tracing was obtained on each of the ten sections, measuring slices from inferior to superior. On an individual image traces were made from medial to lateral. The post-central sulcus was traced on approximately twelve 2mm thick slices measured from inferior to superior across slices and from medial to lateral on each individual slice. The extent of the post-central sulcus was determined by tracing five slices inferior to the origination of the hand-bump and its termination was on the twelfth slice superior to the origination. It was imperative for each ROI to cover the entire sulcus so that all functional activation was recorded. To this end each ROI tracing was thickened to a width of two pixels on each side (4 mm) of the line tracing in order to cover the breadth

of each sulcus fully. Since our voxels were re-interpolated to 2 mm cubed, line thickening produced ROIs that were 8 mm thick (4 mm on either side of the line traced in the sulcus).

Cluster Analysis

After the ROIs were extracted in LOFA using the procedure described, the total number of pixels per cluster within each individual region of interest were examined using AFNI. Threshold correlations of 0.50 and 0.70 were separately applied to the datasets. Overall, three ROIs were measured in each hemisphere for a total of six ROIs per functional run or 54 total ROIs per imaging session. Output files were then imported into Excel (Microsoft Corporation, Seattle, WA) and later SPSS for statistical analysis.

Statistical Analysis of Data

Statistical Analysis of fMRI Data

Data was plotted and examined for any trends or group clusters. Statistical analysis was performed with a repeated measures analysis of variance design to examine variation in the percentage change in each ROI among the groups ($p<0.05$). Post hoc multiple comparisons (Bonferroni-Dunn) were performed to determine which pairwise comparisons contributed to significant main effects.

Statistical Analysis of Behavioral Data

Data was plotted and examined for any trends or group clusters. Univariate distributions of behavioral and performance data were screened for outliers using standardized scores and inspection of box plots of the data. The assumption of normality was checked by inspection of histograms of data and by testing for the

significance of statistics for skewness and kurtosis. The strength of association between fMRI data and behavioral/performance data was assessed using Pearson correlation coefficient with significance tests at the alpha = 0.05 level (two-tailed) unless otherwise indicated. T-tests were conducted on pre-practice scores to determine if a preexisting difference existed between the groups on any of the measures. Pre-practice versus post-practice analysis of variance (repeated measures) was performed to determine how many subjects showed improvement in each dependent measure, these were conducted as a paired-difference t-test.

CHAPTER 4
RESULTS

Subject Compliance, Image Quality Assurance and Exclusions

Subject compliance and follow up were critical determinants of success for this project. Of the 25 subjects initially recruited for the study, 21 subjects returned for a follow up scan. The four subjects who did not return included two from the executed practice group and two from the imagined group. Of the 21 subjects remaining three were excluded due to lack of compliance with the task protocol. Exclusions included one from the executed practice group and two from the imagined group. Subjects excluded due to non-compliance did not complete the required practice sessions at home, having missed at least four sessions without making them up the following day and averaging 11 minutes or less of practice per session. The total time of practice for the excluded subjects was two standard deviations below the mean (mean-2std = 215.46 min) of the included subjects and this served as the main criterion for exclusion among subjects who missed four days or more during the training period. All information regarding the time and dates of practice sessions were self-reported by the subjects enrolled in the study. Specific information regarding excluded subjects is presented in Table 4-1 and 4-2.

Table 4-1. Excluded Subject Demographics and Practice Interval Statistics.

	All Excluded (n=9)	No Repeat Scan (n=4)	Failed Practice Group (n=3)	Poor Technical Quality MRI (n=2)
Average Age (years)	24	25	24	22
Age Range (years)	20-27	20-27	24	20-24
Gender	2 males/7 females	2 males/ 2 females	3 females	2 females
Handedness (Waterloo) Score	0.94 +/- 0.29	0.93 +/- 0.06	0.90 +/- 0.07	1.0 +/- 0.00
Handedness (Range)	0.875 - 1.0	0.875 - 1.0	0.875 – 0.916	1.0

Table 4-2. Subjects Excluded For Failed Task Compliance.

Subject	Total Time of Practice (min)	Total # Days Practice	Total # of Days Missed Practice	Rationale for Exclusion
E13*	0	0	all	Non-compliance
I09	210	20	6	Missed Days > 4
I14	150	20	4	Total Practice Time < 2std from Included Group Mean#

*subject did not perform task at all
(308.94 +/- 46.74)

Review of the subject logs indicated that the instructions to perform the task in a quiet environment were followed by most subjects. Performance was generally conducted in bed before they retired for the evening or while sitting on their sofa in a quiet room. A few subjects performed the task once or twice while riding in the car as a passenger or during a class intermission. These performances were rare and did not make up the majority of any individual subject's trials. Subjects included in the final study practiced for a total average of 310 +/- 47 minutes (range 195-390 min). The number of days of practice averaged 20.8 +/- 3.3 days (range 13-26 days). The number of days subjects missed a session without making it up the following day was 0.3 +/- 1.0 days (range 0-4 days). Subjects clearly performed the task and the average time of practice was approximately three weeks as proposed in the study's methods section.

In addition to evaluation of performance standards, we performed quality assurance studies on the acquired functional and anatomic images used in the study. Image acquisition is a complex technical undertaking that was aberrant in two of the studies performed. These two subjects were excluded due to image acquisition difficulties that made analysis of the functional series unreliable. The assessment that was performed to determine inclusion was a qualitative visual assessment of image quality. After review of all the acquired sequences, two subjects were found to have functional images with large data voids in the center of most images and in regions of

interest important for this study. These subjects were subsequently excluded from further analysis.

Subject Demographics and Practice Interval Statistics

Sixteen subjects were included in the final phases of data analysis. The executed practice group had four males and three females and the imagined practice group had four male and five female members. Each of these subjects had satisfactory performance of the practice task at home and had high quality MR images obtained both during the pre-practice and post-practice phases of the study. A summary of subject demographics, handedness scores and statistics for their self-reported at-home practice sessions are listed in Table 4-3.

Table 4-3. Subject Demographics and Practice Interval Statistics.

	All Subjects (n=16)	Executed Practice Group (n=7)	Imagined Practice Group(n=9)
Average Age (years)	24	25	24
Age Range (years)	21-36	21-36	23-26
Gender	8 males/8 females	4 males/ 3 females	4 males/ 5 females
Handedness (Waterloo) Score	0.92 +/- 0.12	0.92 +/- 0.06	0.93 +/- 0.00
Handedness (Range)	0.83 - 1.0	0.83 - 1.0	0.83 - 1.0
Total Time of Practice (min.)	309 +/- 47	303 +/- 53	314 +/- 44
Total Time of Practice (Range in min.)	195-390	195-350	255-390
Total # Days Practice	20.8 +/- 3.3	19.5 +/- 3.2	22.0 +/- 3.3
Total # Days Practice (Range)	13-26	13- 23	17-26
# of Days of Missed Practice	0.3 +/- 1.0	0.0 +/- 0.0	0.6 +/- 1.3
# of Days of Missed Practice (Range)	0-4	0	0-4

Comparison of the two groups, executed motor practice and imagined motor practice, revealed that the two groups were evenly matched for gender, age and handedness. T-tests comparing subject age between the groups showed no significant difference ($t=0.642$; $p = 0.53$). Similarly, T-tests comparing handedness between the groups failed to reveal a significant difference ($t=-0.082$; $p = 0.936$).

Comparisons were performed to ensure that both groups were evenly matched for the number of days of practice and the total time of practice. As noted in the methods section, subjects in each of the two groups were instructed to practice for fifteen minutes per day until they were recalled for their follow up scan approximately three weeks later. T-tests were used to compare the total number of minutes of practice performed by each group. There was no statistical difference between the two groups in terms of the amount of practice performed ($t= -0.436$; $p=0.67$) or total number of practice days ($t=-0.128$; $p=0.22$). Comparison of the number of days of practice missed without a make up session also revealed no difference between either group ($t=-1.094$; $p = 0.29$). Overall, for the comparison between groups for gender, age, handedness, total hours of practice, total days of practice and missed days of practice there were no statistical differences. These two statistically similar groups were then compared on their physical performance during finger tapping tests.

Finger Tapping Performance Evaluation: Pre and Post-Practice

Finger tapping performance was evaluated so that an independent measure of motor skill improvement could be correlated with any changes noted in cortical activation after the practice period. Subjects spent three weeks practicing the learned sequence either by executing the finger tapping sequence or by using first person

imagery to mentally simulate tapping the learned sequence. The ability of individual subjects to perform motor imagery was a critical factor leading to either the success or failure of the project. To ensure subjects complied with the imagery task and to assess how successful subjects were at performing the imagery, a debriefing session was performed when subjects returned for their follow-up scan. All subjects reported that they were able to accomplish the task of using the first person perspective to practice the finger tapping task. Most subjects reported a gradual learning curve associated with the initiation of imagery. Subjects also reported that the first several days were difficult and required a large degree of effort to concentrate on imagining the task. After several days, however, the imagery was easier to do and resulted in less mental fatigue. The subjects also reported that they felt they were able to improve the rate of imagined tapping for a few days prior to reaching a plateau, after which time they were unable to increase the imagined tapping rate. These findings were uniform among the subjects included for analysis except for subject I19 who reported some difficulty with imagery.

Finger tapping sessions were videotaped to determine baseline (null) and practiced performance. We also evaluated subject performance on two random sequences that were not practiced by either group. Subjects were evaluated using four one minute trials consisting of the practiced sequence repeated twice and two random sequences presented for one minute each. The tapping evaluation was performed before the first scanning session and repeated before the second scanning session which occurred after the three week practice interval. Video taped sessions were analyzed in slow motion for number of completed sequences, number of completed errors and number of self-corrected errors witnessed in each one-minute trial. Completed

sequences were defined as completion of four sequential finger taps that were correctly ordered according to the task sequence. Completed errors were defined as aberrant finger movements that were not halted before completion such as mis-taps, tapping two finger simultaneously, misdirected tapping (missing the finger completely due to poor trajectory), and restarting a sequence before the current sequence was completed. Self-corrected errors were errors that the subject aborted before completion. Typically self-corrected errors were mis-taps that were aborted before the fingers touched.

It was important to develop a single value that reflected the subjects overall performance taking into account both the speed, as evidenced by the number of completed sequences, and the accuracy as denoted by the errors, both completed and self-corrected. Along this line an accuracy index was developed using the following formula: Completed Sequences ÷ ((Completed Errors) + (Self-Corrected Errors/2)). Completed errors were felt to be more serious than self-corrected errors thus the accuracy index weighted completed errors as twice the value of self-corrected errors. The accuracy index was heavily weighted toward the number of errors committed to reflect the idea that increased tapping speed without improved accuracy does not reflect improvement in the subjects performance on the task but merely an ability to move the fingers more rapidly. Pre and post practice accuracy index values for both groups are presented in Table 4-4.

Table 4-4. Finger Tapping Performance Before and After Three-Week Practice Interval (Accuracy Index Values).

	Practiced Sequence			Random Sequence		
Subject*	Null State	3 Weeks of Practice	**Δ null vs. 3 wk practice**	Null State	3 Weeks Without Practice	**Δ null vs. 3 wk interval**
E02	11.07	84.50	**73.43**	7.91	1.74	**-6.17**
E03	5.66	58.80	**53.14**	3.04	3.05	**0.01**
E04	3.50	26.17	**22.67**	1.71	1.80	**0.08**
E06	4.33	8.56	**4.23**	1.47	0.91	**-0.56**
E12	5.07	65.00	**59.93**	5.25	3.24	**-2.01**
E20	2.67	88.50	**85.83**	3.91	1.69	**-2.23**
E25	4.00	53.60	**49.60**	2.36	3.55	**1.19**
I07	2.77	16.31	**13.54**	2.90	3.61	**0.71**
I08	14.00	28.67	**14.67**	31.67	8.83	**-22.83**
I10	10.40	18.67	**8.27**	7.88	3.10	**-4.77**
I11	9.33	67.50	**58.17**	6.67	16.67	**10.00**
I15	2.63	27.50	**24.87**	5.06	3.76	**-1.29**
I16	10.50	17.43	**6.93**	4.74	4.56	**-0.18**
I17	6.58	24.00	**17.42**	14.86	9.33	**-5.52**
I19	34.50	12.76	**-21.74**	7.67	2.91	**-4.76**
I26	1.25	26.00	**24.75**	1.80	3.07	**1.27**

*E=executed practice, I=imagined practice

Individual performance of the practiced sequence as assessed by the accuracy index demonstrated that only one subject (I19) failed to show improvement after the three week practice period. As noted, this subject reported difficulty with the imagery task; however, the subject reported that he did follow the practice requirements thoughout the three week practice interval. The individual performance results on the random sequence demonstrated ten of sixteen subjects had a decrement in performance after the three week interval. The three week inter-scan interval was the time during which subjects rehearsed the practiced sequence either by volitional movement or by imagery; the random sequence was not practiced during this time by either group. Tables 4-5 and 4-6 demonstrate the mean, standard deviation and mean difference for each group, executed and imagined practice, both before and after the three week practice interval for each of the performance variables (accuracy index, completed sequences, completed errors and self-corrected errors). Figures 4-1 through 4-11 show the mean and standard deviation for each group, executed and imagined practice, both before and after the three week practice interval for each of the performance variables (accuracy index, completed sequences, completed errors and self-corrected errors). Comparison of the mean difference for the pre-practice vs. post-practice condition revealed improvement in all performance variables for both groups when subjects performed the practiced sequence. When both groups, the executed and imagined group, performed the random sequence, the results were mixed. During performance of the random sequence the mean difference for both the accuracy index and the number of corrected errors showed a decline in performance; however, the number of completed sequences and the number of uncorrected errors were improved.

A mixed-model ANOVA was performed on the results of the performance testing to determine if any of the noted practice effects were significant for the pre-practice vs. post-practice condition. The ANOVA was also used to determine if the executed practice and imagined practice groups were significantly different on any of the performance variables. Results of the ANOVA evaluating performance on both the practiced and random sequences are shown in Table 4-7. Both groups showed significant improvement in the accuracy index for the practiced sequence ($F=29.09$; $p=0.001$). Both groups showed significant improvement on the number of completed sequences for both the practiced ($F=175.49$; $p=0.0001$) and random ($F=24.03$; $p=0.001$) sequences. The number of uncorrected errors was reduced significantly for both groups on the random sequence ($F=17.45$; $p=0.001$) and the number of corrected errors were significantly reduced for both groups on the practiced ($F=25.92$; $p=0.0001$) and random ($F=7.74$; $p=0.015$) sequences. No significant improvement was noted for the accuracy index during the random sequence ($F=1.65$; $p=0.220$) and the number of uncorrected errors committed during the practiced sequence ($F=3.48$; $p=0.083$).

A group by performance interaction was noted for the practiced sequence for both the accuracy index ($p=0.016$) and the number of completed sequences ($p=0.006$). See Figures 4-3 and 4-6. These interactions were related to the similarity in the performance state between the two groups. This finding was to be expected since the task was novel to both groups during the initial performance evaluation. While the group main effect was non-significant, this finding is superseded by the group performance interaction suggesting that while both groups had significant improvements in the accuracy index and the number of completed sequences, the

executed group performed significantly better than the imagined group on these two performance variables. No other interactions were noted in the data.

A significant main effect of group indicated that the groups were significantly different for uncorrected ($F=7.30$; $p=0.017$) as well as corrected errors ($F=15.11$; $p=0.002$) on the random tapping sequence. In both cases the executed motor practice group committed significantly more errors than the imagined practice group during the follow-up practice session.

Table 4-5. Finger Tapping Performance By Group: Before & After Practice (Accuracy Index & Completed Sequences).

		Accuracy Index			Completed Sequences		
Executed Group		**Pre**	**Post**	**Difference (post-pre)**	**Pre**	**Post**	**Difference (post-pre)**
	Practiced Sequence	5.18+/-2.77	55.02+/-29.15	49.83+/-28.24	34.64+/-5.37	79.71+-11.13	45.07+/-11.10
	Random Sequence	3.67+/-2.29	2.28+/-0.99	-1.38+/-2.43	31.28+/-8.01	37.79+/-5.51	6.50+/-7.94
Imagined Group							
	Practiced Sequence	10.21+/-10.07	26.54+/-16.32	16.32+/-20.94	39.06+/-16.15	66.39+/-14.77	27.33+/-10.65
	Random Sequence	9.25+/-9.21	6.21+/-4.63	-3.04+/-8.79	35.72+/-18.14	45.72+/-13.44	10.00+/-5.56

Table 4-6. Finger Tapping Performance By Group: Before & After Practice (Uncorrected & Corrected Errors).

		Uncorrected Errors			Corrected Errors		
Executed Group		**Pre**	**Post**	**Difference (pre-post)**	**Pre**	**Post**	**Difference (pre-post)**
	Practiced Sequence	3.57+/-1.46	2.07+/-2.03	1.5+/-3.06	8.14+/-4.83	0.71+/-1.07	7.43+/-4.42
	Random Sequence	5.42+/-3.23	10.64+/-4.00	-5.21+/-3.31	10.64+/-5.96	17.00+/-7.05	-6.36+/-9.68
Imagined Group							
	Practiced Sequence	3.83+/-3.81	2.00+/-1.30	1.83+/-3.87	6.39+/-4.88	2.06+/-0.81	4.33+/-4.70
	Random Sequence	3.56+/-2.60	5.39+/-2.71	-1.83+/-3.37	4.67+/-3.39	8.06+/-4.20	-3.39+/-3.78

Table 4-7. Comparison Of Finger Tapping Performance For Executed and Imagined Practice Groups: Pre vs. Post Three Week Practice Session.

Accuracy Index		Performance Main Effect	Group Main Effect	Group Performance Interaction
	Practiced Sequence	F=29.09; p=0.001	F=3.849; p=0.070	F=7.47; p=0.016
	Random Sequence	F=1.65; p=0.220	F=4.436; p=0.054	F=0.23; p=0.637
Completed Sequences				
	Practiced Sequence	F=175.50; p=0.001	F=0.558; p=0.468	F=10.53;p=0.006
	Random Sequence	F=24.03; p=0.001	F=0.974; p=0.340	F=1.08; p=0.316
Uncorrected Errors				
	Practiced Sequence	F=3.48; p=0.083	F=0.013; p=0.912	F=0.04; p=0.855
	Random Sequence	F=17.45; p=0.001	F=7.302; p=0.017	F=4.02; p=0.065
Corrected Errors				
	Practiced Sequence	F=25.92; p=0.0001	F=0.024; p=0.879	F=1.80; p=0.202
	Random Sequence	F=7.74; p=0.015	F=15.11; p=0.002	F=0.72; p=0.411

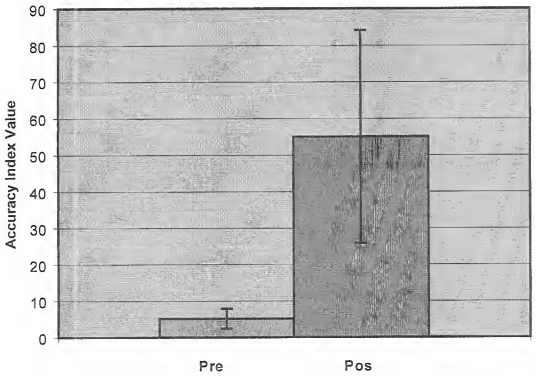


Figure 4-1. Accuracy Index for the Executed Group on the "Practiced" Sequence: Pre & Post Practice (f=29.09; p=0.001).

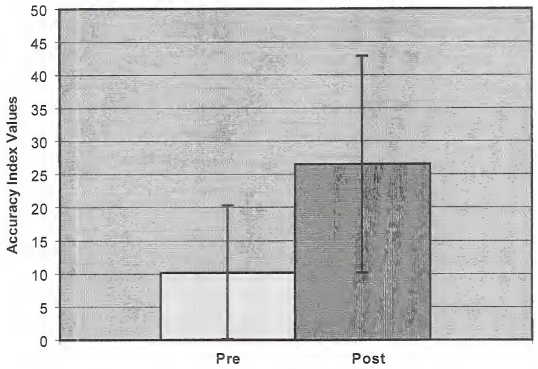


Figure 4-2. Accuracy Index for the Imagined Group on the "Practiced" Sequence: Pre & Post Practice (f=29.09; p=0.001).

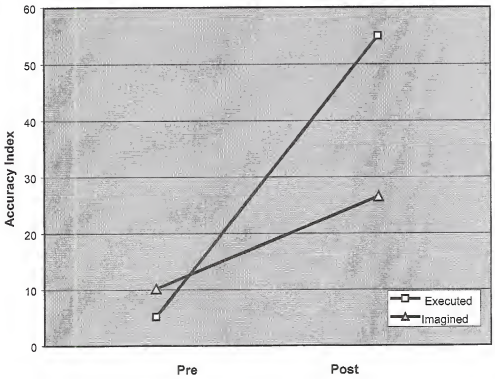


Figure 4-3. Accuracy Index for the Executed and Imagined Groups on the "Practiced" Sequence: Group by Performance Interaction (f=7.47; p=0.016).

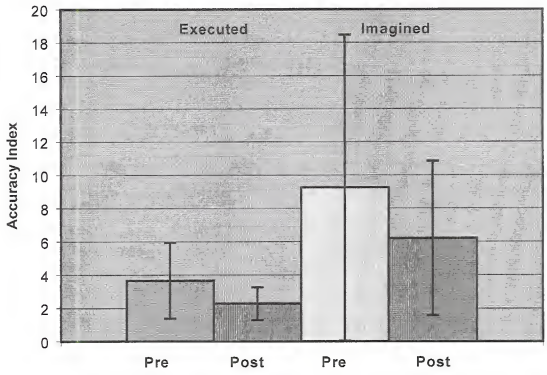


Figure 4-4. Accuracy Index for the Executed and Imagined Groups on the "Random" Sequence: Pre & Post Practice (f=1.65; p=0.220).

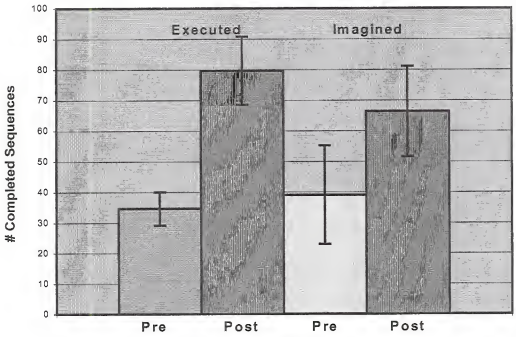


Figure 4-5. Completed Sequences for the Executed and Imagined Groups on the "Practiced" Sequence: Pre & Post Practice (f=175.50; p=0.001).

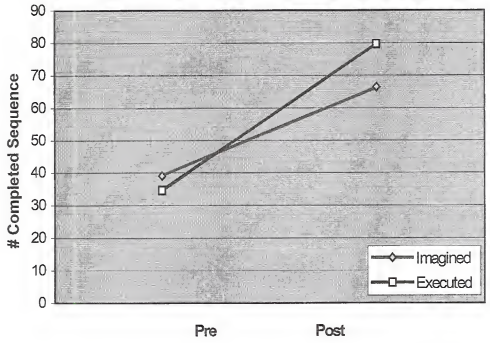


Figure 4-6. Completed Sequences for the Executed and Imagined Groups on the "Practiced" Sequence: Group by Performance Interaction (f=10.53; p=0.006).

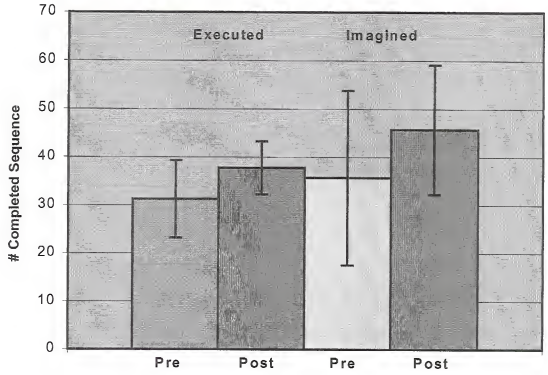


Figure 4-7. Completed Sequences for the Executed and Imagined Groups on the "Random" Sequence: Pre & Post Practice (f=24.03; p=0.001).

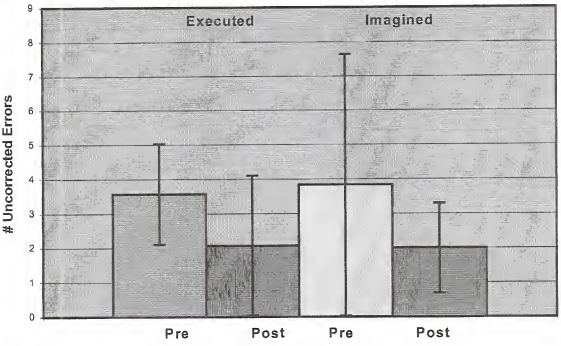


Figure 4-8. Uncorrected Errors for the Executed and Imagined Groups on the "Practiced" Sequence: Pre & Post Practice (f=3.48; p=0.083).

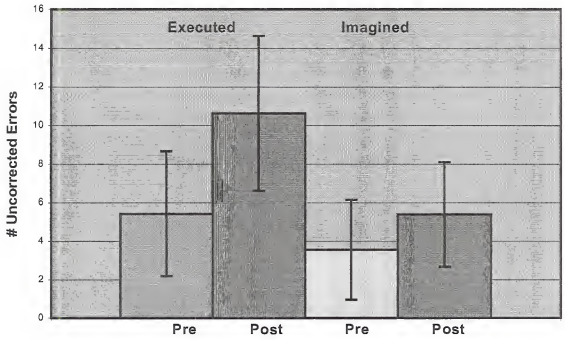


Figure 4-9. Uncorrected Errors for the Executed and Imagined Groups on the "Random" Sequence: Pre & Post Practice (f=17.45; p=0.001).

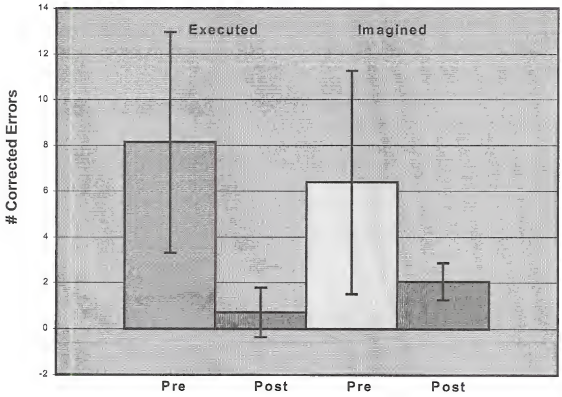


Figure 4-10. Corrected Errors for the Executed and Imagined Groups on the "Practiced" Sequence: Pre & Post Practice (f=25.92; p=0.0001).

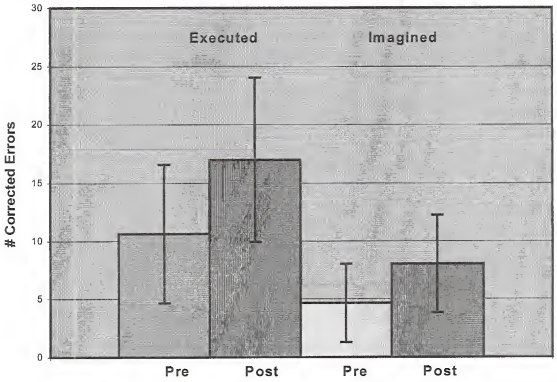


Figure 4-11. Corrected Errors for the Executed and Imagined Groups on the "Random" Sequence: Pre & Post Practice (f=7.74; p=0.015).

Effects of Practice on Cortical Representation

The main focus of this research project was to determine if imagined practice alters cortical representations in a similar fashion to executed motor practice. The study methods called for the evaluation of six regions of interest each with nine functional imaging runs (three each for sequential, practice and random tasks) performed both before and after the three-week inter-session practice interval. The analysis was concerned with determining if practice, either executed or imagined, caused an increase in the cortical representation within a given region of interest. The analysis was performed both on the first run of each of the three series (sequential, practiced, and random) and on the average of all three runs in each series. Data were analyzed at both the 0.50 and 0.70 correlation threshold; however, very few clusters were present at 0.70 and this portion of the analysis was discarded. All data presented are reported for the 0.50 threshold as discussed in the methods section. Secondary analyses were concerned with determining if any trends were evident within an intra-scan session. These types of ordered fluctuations in cluster size might suggest that during repeated trials the subject either habituated to the task or that the initial task run facilitated increased activation on following runs. Lastly, the analysis looked at the correlation between changes in performance and cluster size. It was important to determine if changes in cortical representation were related to changes in subject performance and whether the effects were specific for the tapping sequence used to elicit the fMRI activation.

Raw Cluster Data and Intra-Session Cluster Trends

Table 4-8 demonstrates the cluster volumes for the practiced sequence in the left central sulcus. Likewise, Table 4-9 demonstrates the raw cluster volumes for the random sequence in the left central sulcus. Inspection of the data for both sessions revealed a variable degree of cluster activation ranging from zero activated voxels to over three thousand. Because of the fluctuation a mixed-model ANOVA was performed to determine if the fluctuation occurred in an orderly fashion as the session progressed. Such findings might indicate a trend toward habituation to the stimuli or facilitation of activation as runs progressed. The ANOVA compared clusters in the following order within the three sessions for all regions of interest: the first run against the second run, the second run against the third run and the first run against the third run. Results of the ANOVA demonstrated no significant changes in cluster activation within individual task scanning sessions suggesting that the fluctuation in cluster volume is random within a scanning session and not indicative of habituation or facilitation.

Table 4-8. Pre and Post-Practice Cluster Volumes (mm^3): The Practiced Sequence (Left Central Sulcus).

	Pre-Practice				Post-Practice				Δ Pre vs Post
Subject*	Run 1	Run 2	Run 3	Average	Run 1	Run 2	Run 3	Average	run1/ average
E02	2560	3680	2584	2941	2824	2672	2680	2725	264/-216
E03	1216	1216	1416	1283	1384	1064	792	1080	168/-203
E04	1760	1800	1776	1779	2056	2496	1944	2165	296/386
E06	872	952	952	925	2624	2608	2416	2549	1752/1624
E12	520	784	640	648	1448	1496	1872	1605	928/957
E20	712	992	584	763	2320	3056	728	2035	1608/1272
E25	696	800	856	784	1344	536	392	757	648/-27
I07	832	1320	864	1005	1272	1408	1016	1232	440/227
I08	616	0	0	616	992	1056	480	843	376/227
I10	1576	736	856	1056	1320	1752	1392	1488	-256/432
I11	152	552	336	347	1064	0	1128	1096	912/749
I15	1368	1624	1112	1368	2232	2360	1712	2101	864/734
I16	544	720	760	675	384	2104	1000	1163	-160/488
I17	1376	3096	1744	2072	1656	1424	1552	1544	280/-528
I19	1048	800	1536	1128	0	200	1176	688	-1048/-440
I26	1424	1456	2208	1696	1416	928	1504	1283	-8/-413

*E=executed movement practice, I=imagined movement practice

Table 4-9. Pre and Post-Practice Cluster Volumes(mm^3): The Random Sequence (Left Central Sulcus).

	Pre-Practice				Post-Practice				Δ Pre vs Post
Subject*	Run 1	Run 2	Run 3	Average	Run 1	Run 2	Run 3	Average	run 1 /average
E02	2880	2888	2584	**2784**	2736	3008	2680	**2808**	**-144/24**
E03	720	976	1416	**1037**	776	1056	792	**875**	**56/-163**
E04	2056	1752	1776	**1861**	1320	1432	1944	**1565**	**-736/-296**
E06	1024	1128	952	**1035**	2640	3048	2416	**2701**	**1616/1667**
E12	360	744	640	**581**	1344	1560	1872	**1592**	**984/1011**
E20	1272	600	584	**819**	1128	1016	728	**957**	**-144/139**
E25	528	1328	856	**904**	872	696	392	**653**	**344/-251**
I07	728	848	864	**813**	1136	1240	1016	**1131**	**408/371**
I08	112	0	0	**112**	784	0	480	**632**	**672/520**
I10	800	832	856	**829**	1664	1440	1392	**1499**	**864/669**
I11	304	160	336	**267**	864	1152	1128	**1048**	**560/781**
I15	1720	768	1112	**1200**	1872	3696	1712	**2427**	**152/1227**
I16	1352	352	760	**821**	1400	1200	1000	**1200**	**48/379**
I17	744	1360	1744	**1282**	2440	1816	1552	**1936**	**1696/653**
I19	1296	640	1536	**1157**	1344	1280	1176	**1266**	**48/109**
I26	1512	1296	2208	**1672**	168	704	1504	**792**	**-1344/-880**

*E=executed movement practice, I=imagined movement practice

Left Central Sulcus Analysis

Analysis of variance was performed to determine the effect of practice on cortical representations. Each region of interest was evaluated using a mixed-model ANOVA to determine if a change in cluster size occurred for the first run of each tapping sequence, the average of all three runs of each tapping sequence and whether there was an effect across groups. Table 4-10 and Figure 4-12 demonstrate the results for the left central sulcus comparing the cluster size mean and standard deviation before and after the three week practice interval for run A only. The practiced sequence was the only task to show a significant change in cluster size between sessions. Results demonstrated that cluster size significantly increased for both groups during tapping of the practiced sequence ($F=9.324$; $p=0.009$); however, the increase in cluster size was comparable between the two groups ($F=4.280$; $p=0.058$) with a trend toward the executed practice group having a larger gain in cluster size after three weeks of practice. Although the group effect was not significant, inspection of the data demonstrated that all of the subjects with decreased cluster sizes were in the imagined group. Table 4-11 and Figure 4-13 demonstrate the results of the left central sulcus comparing the cluster size mean and standard deviation before and after the three week practice interval for the average of all three runs. Results demonstrated that the cluster size was significantly larger during tapping of both the practiced ($F=4.599$; $p=0.050$) and random ($F=4.583$;

p=0.050) sequences after the three week interval. Cluster analysis of the average of the three runs for the random sequence was also found to be marginally significant (f=4.599; p0.050), see Table 4-11 and Figure 4-14.

Similar analyses were performed on the right central sulcus and bilateral pre and post central sulci. No significant changes in cluster size were found in any of these regions of interest. Because no change in cluster volumes were found in these areas, they were subsequently dropped from further analysis and were not correlated with changes in performance measures.

Table: 4-10. Cluster Analysis For Run A Only (Left Central Sulcus).

Tapping Sequence	Group	Run A Pre	Run A Post	ΔRun A (post-pre)	Performance Main Effect	Group Performance Interaction	Group Main Effect
Sequential	Executed	1274+/-920	2002+/-926	728+/-1306	F=3.422 p=0.086	F=0.865 p=0.368	F=2.411 p=0.143
	Imagined	1062+/-626	1303+/-680	240+/-782			
Practiced	Executed	1190+/-733	2000+/-618	809+/-650	F=9.324 p=0.009	F=4.280 p=0.058	F=3.731 p=0.074
	Imagined	992+/-486	1148+/-660	155+/-609			
Random	Executed	1189+/-947	1579+/-818	391+/-761	F=2.397 p=0.144	F=0.024 p=0.879	F=0.835 p=0.376
	Imagined	1010+/-530	1270+/-644	260+/-831			

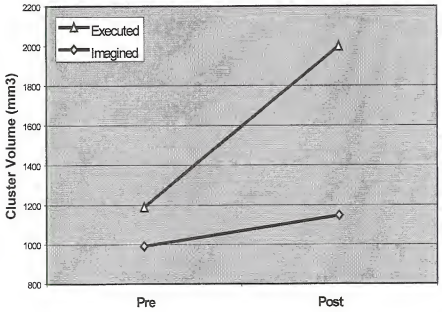


Figure 4-12. Cluster Volumes for the Executed and Imagined Groups on the "Practiced" Sequence: Run A Only (f=9.32; p=0.009).

Table: 4-11. Cluster Analysis For The Average of All Three Runs (Left Central Sulcus).

Tapping Sequence	Group	Average Pre	Average Post	Δ Average (post-pre)	Performance Main Effect	Group Performance Interaction	Group Main Effect
Sequential	Executed	1115+/-825	1931+/-825	517+/-875	F=2.905 p=0.110	F=0.876 p=0.365	F=2.212 p=0.159
	Imagined	1201+/-581	1351+/-389	151+/-695			
Practiced	Executed	1303+/-821	1845+/-734	542+/-745	F=4.599 p=0.050	F=1.556 p=0.233	F=2.308 p=0.151
	Imagined	1061+/-604	1204+/-490	143+/-54			
Random	Executed	1210+/-863	1602+/-853	391+/-663	F=4.583 p=0.050	F=0.091 p=0.767	F=1.287 p=0.276
	Imagined	967+/-414	1319+/-573	352+/-658			

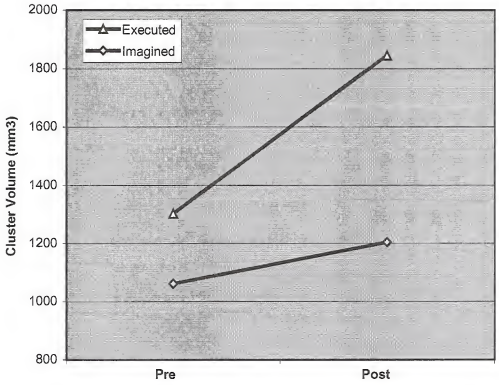


Figure 4-13. Cluster Volumes for the Executed and Imagined Groups on the "Practiced" Sequence: Average of the Three Runs (f=4.59; p=0.05).

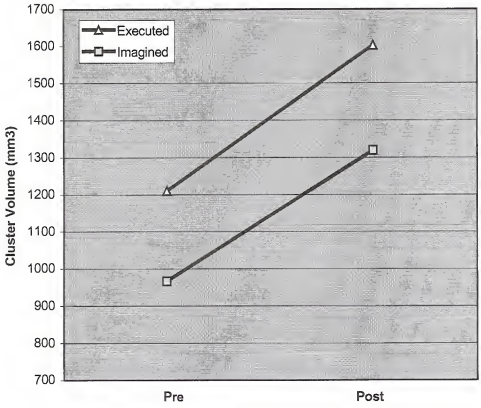


Figure 4-14. Cluster Volumes for the Executed and Imagined Groups on the "Random" Sequence: Pre & Post Practice (f=4.58; p=0.05).

Correlation of Practice Measures and Cluster Volume

To ascertain the relationship between performance gains and the changes noted in cluster volume after practice, Pearson correlation coefficients were calculated. The correlation analysis was limited to the left central sulcus since this was the only region of interest where significant changes in cluster volume were noted. As discussed, significant changes in cluster size were found when both groups, the practiced and imagined groups, performed the practiced and random sequences. The change in cluster size during run A of the practiced sequence and during the average of the three runs for both the practiced and random sequences were evaluated for their correlation with practice variables including the accuracy index, number of completed sequences, completed errors and self-corrected errors. To assess the individual correlations by group, the analysis was performed on both the mean difference scores for the executed and imagined groups and also on the combination of the two groups. Correlation results are shown in Table 4-12.

Table 4-12. Performance Changes vs. Left Central Sulcus Cluster Volume Changes.

Experimental Group	Δ fMRI Cluster Volume by Tapping Sequence & Run	Performance Measure	Correlation
Executed	Practiced (run A only)	Δ Accuracy Index (practiced sequence)	N/S# r= -0.127 p=0.785
Imagined	Practiced (run A only)	Δ Accuracy Index (practiced sequence)	r=0.857 p=0.003
Combined (executed & imagined)	Practiced (run A only)	Δ Accuracy Index (practiced sequence)	r=0.528 p=0.036

All other correlations between changes in cluster size and performance including completed sequences, error and corrected error rates were non-significant

Correlation analysis demonstrated that changes in cluster size for both the imagined ($r=0.857$; $p=0.003$) and combined (executed and imagined, $r=0.528$; $p=0.036$) practice groups were significantly correlated with performance gains. These findings were specific for the change in cluster size noted for run A only of the practiced sequence and for performance changes as measured by the accuracy index. No other correlation coefficients reached significance including comparisons of the averaged cluster size for the practiced sequence, cluster size change for run A only of the random sequence, the averaged cluster size change for the random sequence, and the performance variables: number of completed sequences, uncorrected errors and corrected errors.

Of interest is that the executed group, while showing a significant change in cluster size for run A, did not show a significant correlation with any of the performance measures. Figure 4-15 shows the change in cluster size for run A of the practiced sequence vs. the change in the accuracy index after three weeks of practice. Figure 4-16 demonstrates the linear regressions performed to evaluate the association between the change in cluster size and the change in the accuracy index for the executed, imagined and combined groups.

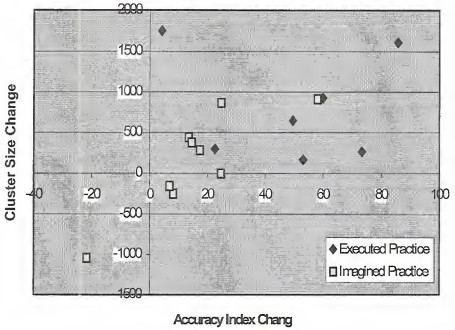


Figure 4-15. Change In Cluster Size vs. Change in Accuracy Index.

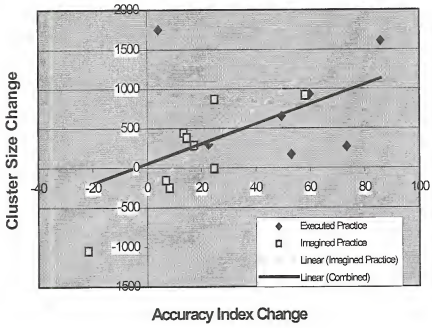


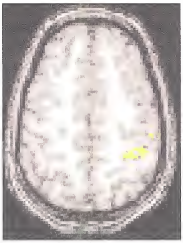
Figure 4-16. Change in Cluster Size vs. Change in Accuracy Index: All Groups.

Summary of Findings

In summary, three major findings emerged from these results. The first finding was that both the executed and imagined practice groups demonstrated a significant performance improvement after three weeks of practice; however, the executed group improved significantly more than the imagined group on the practiced sequence as assessed by the accuracy index and the number of completed sequences. Both groups improved equally on the number of corrected errors. Tapping speed appeared to generalize as both groups displayed better performance on the random sequence in terms of the number of completed sequences. The number of uncorrected and corrected errors; however, both increased significantly after the three week interval on the random sequences for both groups. The executed group's error rate was significantly higher than the imagined group for both of these variables. The second major finding was that the left central sulcus was the only region of interest to demonstrate a significant enlargement in cortical activation after practice. These changes appeared to be similar for both the executed and imagined practice groups. The increase in cortical activation was limited to the first and averaged runs of the practiced sequence. Additionally, a marginally significant increase in the volume of cortical activation was also observed for the averaged run of the random sequence. The third major finding was that the accuracy index of the practiced sequence was significantly correlated with the pre-post difference in cluster volume. This relationship was due to the strong correlation amongst the

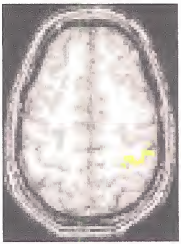
imagined group. A significant correlation was not observed between performance and cluster size for the executed group.

In summary, subjects who performed imagined practice demonstrated increases in cortical activation that were correlated with improvements in actual finger tapping performance. These findings were specific to the changes in cluster size during run A of the practiced sequence and the accuracy index obtained during performance of the practiced sequence. Pictures 4-17 and 4-18 show the cluster changes before and after rehearsal of the "practiced" sequence for both an executed and imagined practice subject.

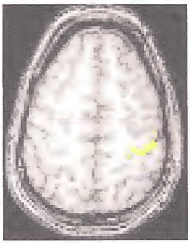


Inferior Slice Pre-Practice

Inferior Slice Post-Practice



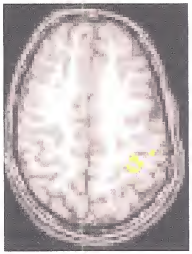
Superior Slice Pre-Practice



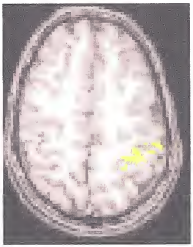
Superior Slice Post-Practice

Total Cluster Size Pre	**Total Cluster Size Post**	**Total Cluster Size Change**
1368	**2232**	**864**
Accuracy Index Pre	**Accuracy Index Post**	**Accuracy Index Difference**
2.63	**27.50**	**24.87**

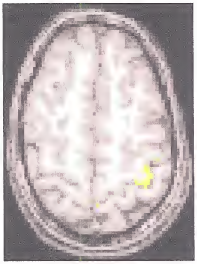
Figure 4-17. Imagined Practice Group Subject 15 Pre and Post "Practiced" Sequence (0.50 threshold).



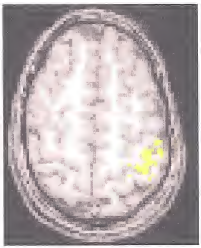
Inferior Slice Pre



Inferior Slice Post



Superior Slice Pre



Superior Slice Post

Total Cluster Size Pre	Total Cluster Size Post	Total Cluster Size Change
712	2320	1608
Accuracy Index Pre	**Accuracy Index Post**	**Accuracy Index Difference**
2.67	88.50	85.83

Figure 4-18. Executed Practice Group Subject 20 Pre and Post "Practiced" Sequence (0.50 threshold).

CHAPTER 5
DISCUSSION

Project Goals and Hypothesis Reviewed

Motor imagery has a long history and is touted by many notable figures in athletics for the performance gains it provides. As elegant studies by Nudo and colleagues (1996) have demonstrated, practice induces changes in cortical representation. Evidence was sought in this investigation to support the hypothesis that performance gains noted with imagery are also the result of changes in cortical representations. The original hypothesis stated that both executed and imagined practice should increase cortical representations after subjects practiced a specific finger tapping sequence for three weeks. The changes in cortical activation seen after imagery were hypothesized to be smaller than those associated with executed motor practice. Additionally, the changes were hypothesized to be specific and limited to the sequence that was practiced and would not extend to other finger tapping sequences or patterned movements. The following discussion will be based on these hypotheses and the findings from the current study of motor imagery and cortical reorganization.

Motor Performance Following Executed and Imagined Motor Practice

Finger tapping speed and accuracy were assessed to provide an objective measure of changes in motor performance. The executed and imagined practice groups were hypothesized to have an improvement in performance scores after three weeks of practice. The degree of change was thought to favor the executed practice group. Additionally, subjects in both groups were hypothesized to improve their speed and accuracy on the practiced sequence but show no improvement when presented random sequences. Random sequences were introduced to determine if practice effects generalized. Performance on both the practiced and random sequences were analyzed by comparing the number of completed sequences, uncorrected tapping errors and corrected tapping errors both before and after the three week practice period. An accuracy index was also developed that heavily penalized the subjects for errors committed during the performance testing. This index was used to indicate not only improvements in speed, but more importantly to take into consideration improvements in accuracy which were considered markers for task learning. A basic premise was that speed without accuracy should not be considered indicative of performance improvement.

Study results demonstrated that both the executed and imagined groups improved after practice. Improvement was noted on the practiced sequence as indicated by the accuracy index, number of completed sequences and the corrected error rate. While both groups significantly improved on these performance variables, a significant group by performance interaction suggested that the executed

group sustained a significantly greater improvement in terms of overall accuracy as well as a greater increase the number of completed sequences as compared to the imagery group. Both groups also demonstrated improvement in the number of completed sequences on the random task; however, the number of uncorrected and corrected errors were significantly increased relative to their pre-practice levels. Because of the large number of errors, the accuracy index for the random sequence showed no significant change after practice. Additionally, a group main effect was noted indicating the executed group committed significantly more uncorrected and corrected errors compared to the imagery group during performance of the random sequences. Prior to addressing the main findings related to imagery and the practiced sequence, the unexpected findings that were obtained during the random tapping performance evaluation will be discussed.

Unexpected Findings for Random Sequence Performance

As noted, the random sequences were introduced to determine if the practice effect generalized, resulting in improved performance on tasks novel to the subject. Contrary to our initial hypothesis, the results demonstrated both groups improved significantly in the number of completed random sequences they were able to perform. These unexpected results may simply represent that subjects were more accustomed to moving their fingers rapidly after rehearsing the practiced sequence for three weeks. During debriefing sessions subjects indicated that they found alternating finger tapping sequences more familiar and easier to perform than during the initial performance session. It seems likely that subjects felt more comfortable

trying to perform the tapping sequence rapidly; however, the increased speed was not matched with accurate movements. This statement is supported by the finding that subjects in both groups had a significant increase in the number of uncorrected and corrected errors as seen on the videotapes taken during the performance sessions. Additionally, the results demonstrated that the executed group committed significantly more errors than the imagery group during performance of random sequences. These findings suggest that while the subjects were able to move their fingers faster, as evidenced by the increased number of completed sequences, the accuracy during the random tapping session was reduced. Review of the performance session videotape offers some explanation. On video many subjects seemed to be overly confident in their ability to move quickly. This confidence may have been fostered by having subjects perform the practiced sequence first during the follow-up performance session. Typically subjects improved so dramatically on the practiced sequence that it might have transformed into a heightened sense of confidence to perform the random tapping sequence; however, this was not the case. The videotape clearly showed subjects having difficulty shifting from the practiced sequence to the random sequences. The executed group attempted to move faster as a whole and these subjects made significantly more errors during the random tapping session. An analogy that might apply is overdriving your headlights on a dark road. Subjects attempted to move faster than their motor system could accurately control. Even though subjects performed the sequence more rapidly after the three-week interval, it is not likely that these changes represent a generalization of the learning

that occurred on the practiced sequence. The accuracy index did not significantly change for either group on the random task and a stringent definition of improved performance should take into account both increased speed but more importantly improved accuracy. The random task performance did not obtain both of these goals thus the null hypothesis is validated; no increase in overall performance on the random task for either group.

Significant Improvement on the Learned Sequence

While the random sequence result demonstrated increased speed but diminished accuracy, both speed and accuracy were improved on the practiced sequence. The results further demonstrated that while imagery was capable of providing significant gains for both of theses measures, the gains obtained by actual execution of the practiced sequence were significantly larger. Although these findings were predicted by the hypotheses of this project, they differed from the results of Sirigu, et al. (1996), who found mental rehearsal nearly equated with executed practice [101]. Sirigu's study differed from the present one in that no training period intervened between imagery and assessment, both were performed on the same day. Another important difference is that Sirigu had imagery subjects orally report their imagined performance but actual performance was not tested. From the current study, it seems likely that subjects overestimate their abilities; therefore, a self-report of imagined performance is not a substitute for having the examiner visualize the performance directly.

A major finding from the performance data was that the executed and imagined groups had significantly different performance gains after practice. This difference in performance between the two groups raises many interesting questions about performance strategies and basic neuronal mechanisms underlying motor learning. While the current study did not directly address these issues, the mechanisms by which imagery can promote learning and affect behavior are most intriguing and warrant extensive discussion. The mechanisms proposed in the following discussion represent hypotheses for future research endeavors and appropriate studies to address these questions will be proposed.

Proposed Neurocognitive Mechanisms For Executed and Imagined Practice

The current study has demonstrated that executed and imagined motor practice can lead to significant improvements in performance of the practiced sequence. The critical neural mechanisms by which these changes occur may be similar; however, the sensory input and feedback that refine the developing motor program may be different in the two conditions. The following discussion will explore this comparison and attempt to provide a hypothetical reason for the difference in learning performance between the two groups on the practiced sequence.

Mechanisms for the difference between the two groups may range from attentional mechanisms to differences in the strength of the sensory stimuli delivered to the motor programming areas. The neuronal signaling of sensation during the execution of a motor routine may be present and incoming at all times and may be

modulated by the selective attention of the subject. Motor practice may be something that can be accomplished independent of complete focused attention. Executed practice may generate robust sensory feedback while imagery produces less robust sensory feedback. Overall, imagery may interact with the motor programming areas in a different fashion. During imagery, the ability to engage the motor system and the developing motor routines are wholly dependent on the subject's ability to perform imagery and focus attentional mechanisms on the task. In the imagery condition, the only sensory feedback to the developing motor program may be the sensory feedback willfully generated internally by the subject based on prior sensory experience. Executed motor practice, by contrast, may occur in settings where distractions shift attention away from the task. The sensory input would still be directed toward the motor system even though it was out of direct conscious awareness. The same luxury is likely not afforded to subjects wanting to improve performance through the use of imagery. The mechanisms by which these factors affect the production and refinement of the motor programs are undoubtedly complex, however, the next section will provide some possible models for the interactions suggested above. Possible future studies to address these models will also be detailed.

Proposed Factors Influencing The Motor Program That Affect Performance

Sensory Input

The reasons for the significant difference in performance gains between the executed and imagined groups are unclear but several mechanisms will be proposed

including variation is the strength of sensory input to motor programming areas, ability of subjects to perform vivid imagery and attentional mechanisms. The first mechanism may be that execution of a motor task provides more robust sensory and proprioceptive feedback to the cortex and subcortical structures implicated in motor learning. The execution of movement stimulates the somatosensory cortex by way of proprioceptive feedback from joint and cutaneous receptors. This information is not only relayed to the somatosensory cortex but also becomes integrated by way of the thalamus and putamen into the subcortical motor routine. The strength of sensory input to the striatal motor subsystem may be greater for executed vs. imagined motor movements. This increase in either neuronal firing rate or recruitment could facilitate a more robust and accurate rate of refinement of the motor program. Passingham (1993) discusses the integration of proprioceptive information and its assimilation in parietal cortex with the transfer and use of the proprioceptive coordinates by the lateral premotor cortex and basal ganglia during the selection of movements during procedural learning tasks [60]. The strength of input may affect the strength of subsequent connections and subroutines developed by the basal ganglia that are used to support the learned sequence. The specificity of the proprioceptive coordinates developed from repeatedly tapping one sequence may explain why the gains in accuracy are specific to the sequence practiced and not generalized to other novel finger tapping sequences. Pascual-Leone, Grafman, and Hallett (1994) discussed the role of the basal ganglia in developing and maintaining an explicitly learned motor routine [120]. They suggest that once the basal ganglia

was effectively engaged, it was able to subserve the majority of the motor program for these types of automated movements. Mapping cortical representations, they noted that the cortical maps developed using transcranial magnetic stimulation (TMS) regressed to pre-practice levels as learning proceeded within a single experimental session. The authors suggested that as a motor sequence was explicitly learned, the contribution of the cortex attenuated, with other areas such as the basal ganglia assuming more active roles in the execution of the movement. These findings seem to contradict the current study which suggested cortical representations expand with long-term practice. It seem as though Pascual-Leone misinterpreted their findings based of the work of Karni, et al. (1995) who found short term learning effects, or what they referred to as "fast learning" reduced cortical activation as subjects initially habituated to the task [5]. Karni et al. later provided evidence that in the same subjects, long-term practice leads to expansion of the cortical representations. Even though the TMS results seem incorrectly interpreted, Pascual-Leone's original hypothesis regarding the role of the basal ganglia may by true. Based on this portion of the mechanism posited , one may reasonably speculate that by increasing the neuronal input from the somatosensory cortex, more continuous and robust stimulation of subcortical structures occurs stimulating the formation of discrete subcortical motor routines. Stated another way, by providing a continuous drive toward the basal ganglia, it may be possible to enhance or facilitate the development of efficient subroutines that support the learned movement. The tonicity or drive provided by executed movement would

likely be more robust and sustained for a longer period of time than the situation produced by the use of imagery alone. This hypothesis would favor the performance of executed motor practice over practice by imagery and could be one neuronal mechanism to explain the discrepancy in performance noted during this study.

Cognitive Learning: Verbal To Motor Transition

A second factor that is important to consider is that subjects often reported that they first used internal verbal cues to facilitate accurate task performance; however, verbal cues were quickly dropped as the task became more automated. The coupling of verbal cues to motor action may initially promote accuracy during fast learning; however, as the task becomes more automated a transition may occur from cognitive, fast learning to automated, slow learning. It may be that fast learning is within the bounds of cognition while slow learning is modulated at a level outside of conscious awareness. The initial reduction in cortical area may be caused by an increased dependency on verbal areas outside of the motor cortex that moderate the task. One may speculate that as task learning develops, less verbal integration is needed and motor systems are able to independently refine the task based on sensory feedback alone. This may lead to increased cortical representations as noted in the prior studies as motor programs are refined and local circuitry reorganized to support the task. Cognitive learning mechanisms may also be relevant for imagined practice throughout the course of training, since imagery may require a verbal, as well as a sensory component, to maintain selective attention toward the task. Sensory experience may only be remembered in the context of

verbal associations making the sensation of movement and the verbal representation of that sensation inextricably linked. This suggestion may mean that imagery does not allow a complete transition between verbal and pure motor learning. Therefore, imagery may have limitations in the degree of cortical reorganization that is possible especially if large scale reorganization is highly dependent on pure motor learning and rehearsal that is accomplished outside of direct consciousness.

Imagery Competence

A third factor that may explain the discrepancy in performance noted during this study involves an over-learned vs. seldom used task; finger tapping and imagery, respectively. Vivid, detailed imagery is typically not part of daily experience unless you are an Olympic athlete training for competition. An important factor that may explain the discrepancy between executed motor practice and imagined motor practice is the ability of the individual subject to perform mental imagery competently. Subjects were instructed to perform imagery using the first person perspective. In other words, subjects should have attempted to feel the movement as though it were actually occurring and to visualize the body part from their own perspective, not as if they were looking into a mirror. All of our subjects reported that they were able to accomplish the task; however, the degree of competency was likely different among the subjects included in the study. All subjects underwent a post-experiment debriefing that included questions regarding the difficulty of performing the imagined movement. They reported a steep learning curve with several subjects noting that imagery was initially very difficult to perform especially

for the allotted fifteen-minute practice interval. A discrepancy was noted in the self-reported performance gains during imagery, with several subjects reporting continual improvement in imagined movement speed and accuracy while other subjects noted a definite performance plateau. One subject (I19) commented that she didn't feel as though she improved her task performance using imagery after the first few days. This subject described performing imagery by using a numeric system applied to each finger in that she would count the fingers as she moved through the sequence. This subject felt her performance did not improve and when asked to tap the practice sequence for one minute during her follow-up performance exam she demonstrated a decrease in the accuracy index compared to pre-practice levels. She was the only imagery subject that failed to make significant performance improvements on the practiced sequence. An important corollary, discussed in more detail later, was that her performance decrement correlated with a reduction in her post-practice activation volumes. Subjects with the most robust improvement noted they performed imagery that was vivid and detailed. These subjects reported that they could feel and sense the movement of their fingers. One subject even noted that he could tap faster using imagery than during executed movement.

Unlike the execution of a motor task, which is an all-or-none phenomenon, the induction of imagery is likely a skill that has a broader range of proficiency in the population. Paivio (1995) notes that variables such as the goals of the task, the skill level of the performer and the purpose of the imagery intervention are all critical in determining the success of the imagery [179]. Imagery skills were not a

factor in determining subject inclusion or assignment in this study. All subjects who passed the exclusionary criteria were enrolled. Thus the imagery abilities of our subjects were not known. In fact, the first time insight into their abilities was gained was during the post-practice debriefing at the conclusion of the study. Clearly this is one limitation that needs to be addressed in future work. Debriefing sessions elucidated differences in the ability to perform detailed imagery; however, while some subjects felt imagery was difficult, the group's overall self-reported ability to perform vivid imagery likely contributed to the performance gains noted. Future studies addressing the feasibility of using imagery to improve performance should extensively evaluate subjects for the ability to perform vivid imagery since it clearly was a critical determinant of success for this group as a whole.

Selective Attention

While the innate ability to perform imagery has been discussed and its importance validated, a fourth critical component to successful imagery must be addressed; namely attention. Unlike executed motor practice, which can be done while engaged in other cognitive tasks, imagery requires that a tremendous amount of attention be directed toward the imagined activity. Our design incorporated a fifteen-minute imagery session; however, several subjects regarded this time period as too long to maintain their complete attention. Attentional mechanisms have been implicated in the production of imagery by Decety et al. (1996), and it is likely that lack of selective attention toward the task limited the effect that could have been achieved [94]. Cortical areas implicated by Decety et al. in imagery include the

medial prefrontal cortex, anterior cingulate gyrus, supplementary motor area, and lateral parietal cortex. These cortical areas may modulate imagery through their involvement in executive control, working memory, preparation to respond or intention, as well as other mechanisms. It is logical to assume that any reduction in attention toward the imaging task would have direct consequences on the effectiveness of the practice sessions. Clearly a subject with the ability to concentrate for prolonged periods without distraction would have an advantage over a subject who only focused attention on the task for a brief period of time. The difficulty in maintaining a prolonged period of focused attention on the imagery task could be a major contributor to the differences seen between the imagery group and the executed motor practice group. In future studies, it may be advisable to limit the practice periods to encourage full attention toward the task.

Physical and Imagined Flexibility and Range Of Motion

An additional issue with imagery is one of flexibility and range of motion. Since imagery does not promote motor output, subjects may have the mental capacity to image the movement but lack the physical agility to accomplish the brain's will. Along this line, it was noted that two of the imagery subjects did not perform the executed movements using a full range of finger movements. Their performance was accurate and fast, but the degree and range of finger flexion and extension was less than the other subjects in the study. It is unknown whether these subjects imagined the finger tapping using these truncated movements or whether the truncated movements were the physical manifestation of poor flexibility and

decreased range of motion. Overall, it seems logical that to obtain the most robust results from imagery, subjects must attempt the most vivid representation of the scene and the sensations as possible. Therefore, it may be more beneficial for subjects to err on the side of overproducing the movement versus under representing the full breadth of the movement sequences. Subsequent studies may benefit from providing subjects with detailed instructions and training regarding how to perform imagery correctly.

Newer Strategies for Motor and Imagined Learning

Recent research has demonstrated certain learning techniques may promote more robust motor learning. McNevin et al. (2000) have shown that directing learners' attention to the effects of their movements can be more beneficial for learning than directing their attention to the details of their own actions [180]. Furthermore, giving learners some control over the training regimen has been found to enhance learning, unlike prescriptive training protocols that dictate when feedback will be delivered, how often, and the order that tasks will be practiced. The instructions to subjects in this study to perform the sequences for fifteen minutes per day may not be the best method of ensuring compliance and the effect of long practice sessions may be mental fatigue. Future studies using motor imagery may want to define total practice by the number of repetitions vs. total time of practice. Conversely, it may be more beneficial to practice for short periods increasing the overall number of sessions to keep the final total time of practice the same. Finally, McNevin et al. suggest that practice in dyads (or larger groups) can result in more

effective learning than individual practice sessions. If possible in future studies, it would be beneficial to have subjects practice the executed or imagined tapping in a controlled, group environment. This would not only promote performance gains but would allow for better assessment of subject compliance.

Summary of Performance Findings and Supporting Mechanisms

To review, the executed and imagined practice groups both demonstrated significant improvements in performance, which were specific for the practiced sequence. While some imagery subjects made significant performance gains, the mean improvement was less than with executed motor practice. The difference between groups could be due to several factors. First, imagery may not provide robust stimulation of the subcortical structures implicated in procedural learning and the execution of highly learned motor routines. Second, there was a notable difference in the subject's innate abilities to perform imagery that might have affected the performance gains of the imagery group as a whole. Lastly, attentional mechanisms are critical to successful imagery, and subjects in the imagery group may not have been able to devote selective attention to the task for the required fifteen-minute practice interval thus limiting the results. Regardless, significant performance improvements after imagined practice both in the number of sequences completed but more importantly in the degree of accuracy were noted. While these changes were not as robust as the executed practice group, the potential of imagery opens up significant research opportunities in many arenas including neurorehabilitation. The findings of performance gains are but half of the story. The

question of whether performance improvement translates into evidence of cortical plasticity will be addressed in the following section.

Practice Induced Expansion of Cortical Representations

Rationale and Findings Reviewed

A major goal of this research was to adopt the concepts of Nudo and colleagues (1990,1996) and investigate the role of neuroplasticity in motor learning in human subjects. Nudo et al. presented several studies that demonstrated the ability of the cortex to undergo reorganization in response to stimulation of the cortex or execution of movement routines [4, 93, 124]. More recently an elegant study was undertaken by Karni et al. (1995), providing an experimental framework for the present study. Karni, et al., used fMRI to demonstrate that motor practice results in enlargement of cortical representations in primary motor cortex [5]. The current study was based on these findings and the assumption that imagery probably shared many of the same neural pathways as volitional, executed movement.

An underlying assumption was that imagery shared the same underlying cortical representations and motor sequencing routines as executed movement. This assumption was based on the work of Decety, Crammond and Cohen among others, who speculated that imagery likely shares the same neural substrate as the machinery of primary sensation and action [80, 95, 96]. Next it was assumed that if imagery shares the same neuronal circuitry as executed movements, then the likelihood was that imagined practice should alter cortical representations in the same fashion as executed practice. Based on these hypotheses, subjects were randomly assigned to

one of two groups, either the executed or imagined practice groups. Imaging was performed before and after the practice interval. Several regions of interest were analyzed including the central sulcus, precentral sulcus and the postcentral sulcus, all bilaterally.

Analyses revealed significant changes in cluster volume only within the left central sulcus. Results for the left central sulcus demonstrated a significant increase in cluster size between the pre and post-practice condition for the practiced sequence for both the first run (run A) and the average of the three runs. No statistical difference was noted between the executed or imagery group for either of these significant findings. An unexpected finding was that there was a pre-post change on the averaged cluster size for the random sequence as well.

The results of this portion of the study were remarkable and validated our hypothesis that imagined practice can induce changes in cortical representation. Findings from the current study also replicated the early work of Karni, et al. demonstrating increased activation of primary motor cortex after executed practice [5]. Interestingly, the increase in cluster volume was not statistically different between the two groups, indicating that both executed and imagined practice promoted increases in cortical activation. However, the increase in activation was largely driven by the executed group since the imagery group only demonstrated five out of nine subjects to have an increase in cortical activation after practice. As will be discussed, the five subjects who showed increased activation all showed improved performance on the accuracy index. The results suggest that if subjects

performed robust imagery that lead to improved performance, then those findings correlated with increased cortical activation. Executed practice lead to more robust performance gains and these gains translated into changes in cortical activation in most of the subjects. The mechanisms giving rise to these findings are interesting and lead to provocative speculation as to the meaning of the changes seen with either mode of practice.

Proposed Model For Practiced Induced Cortical Reorganization and Supporting Background

The finding that imagined practice changes cortical representations suggests that the neural substrate underlying imagery is in fact similar to the neural substrate that facilitates executed movement. Karni et al. (1995) suggested that the neural mechanisms responsible for the changes in cortical representations after long-term [executed] practice are based on improved "synaptic connections between task-relevant units sub-serving the execution of the acquired skill" (p. 157) [5]. Based upon this description, one may speculate that the increased cortical representations reflect an underlying mechanism by which the primary motor cortex becomes primed to execute the specific motor sequence rapidly and efficiently. As will be discussed in the next section, there was a high correlation between improved performance and changes in cluster size. The local reorganization within primary motor cortex may facilitate improved performance and accuracy by having a dedicated or semi-dedicated local circuit that supports the specific practiced sequence. It would seem reasonable that since resources are not limitless, the brain

acts to shift neuronal resources toward tasks that are commonly performed. While the primary motor cortex is well known as the site from which efferent motor signals are generated, Alexander, Delong and Strick (1996) suggest that the primary motor cortex may have a role in developing the motor program directly through connections with the basal ganglia [67]. Changes in cluster size may be attributable to two factors. As discussed, local reorganization may be used to facilitate the rapid integration and efferent signaling of the motor program. A second mechanism may be related to the primary motor cortex's role in the motor circuit described by Alexander, Delong and Strick and how this role helps refine the practiced motor sequence.

Marsden suggested that the basal ganglia are implicated in the execution of complex simultaneous and sequential movement [79]. Likewise, this system has profound implications for procedural learning. How the basal ganglia can effect improved performance is not clear and less certain is the role of primary motor cortex in this process. Alexander, Delong, and Strick proposed a "motor circuit" centered on the putamen that incorporates direct projections arising from the motor cortex [67]. The motor loop they proposed allows for the integration of not only primary motor but sensory information in a topographically organized fashion. The loop ultimately proceeds back to the supplementary premotor area by way of the globus pallidus, substantia nigra and the thalamus. This circuit allows information about motor performance to be integrated, analyzed and corrected so that motor programs returned to the supplementary motor area are more accurate. The current

study utilized imagery to effect performance changes. As proposed, imagery utilizes the same basic pathways as executed movement but the exact location of the sensory input may not be the same. Imagery likely utilizes memories of movement sensation but where these are stored and how they are ultimately integrated into the motor loop are unknown. Representations of sensation may enter along the pathway of the primary sensory projections or from more rostral areas such as the medial premotor cortex, an area concerned with the internal generation of action. Wherever these sensations are integrated, they act to constrain and reform the motor program leading to improved motor performance.

While sensory feedback is critical, the role of the primary motor cortex may be of equal importance. The primary motor cortex has direct efferent connections not only to the spinal cord but to the putamen. As the motor program is produced and executed, signals are sent to the basal ganglia that are integrated into the motor loop and subsequently modulate the next movement. The efferent leg of the motor loop terminates on the supplementary motor cortex; however, this area has direct projections to the primary motor cortex and can influence complex movement. Alexander, Delong and Strick (1996) suggest the loop terminates at the supplementary motor area; however, this area has direct projections to the primary motor cortex [67]. A logical extension of the model based on anatomical connections would suggest that the closed loop may originate and end with the primary motor cortex utilizing the supplementary motor area as an intermediate synaptic junction . This model of a primary motor cortex-basal ganglia closed circuit loop may be one

mechanism by which motor programs are refined and later stored in primary motor cortex. Modulating synaptic connections from the supplementary motor area may promote reorganization of the primary motor cortex. A feedback loop may be generated that begins with the production of movement or robust imagery and the resulting sensations these tasks generate (executed movement may also contribute via direct connections from primary motor cortex to the putamen). This motor and/or sensory information is utilized by the basal ganglia to refine the motor program and it ultimately returns the refined motor program to the primary motor cortex where it promotes localized reorganization. The refined local primary motor cortex circuitry is then capable of producing highly efficient, but more importantly, accurate movements. This process is repeated during each repetition of the movement promoting improved performance. A schematic of the proposed system is presented in Figure 5-1.

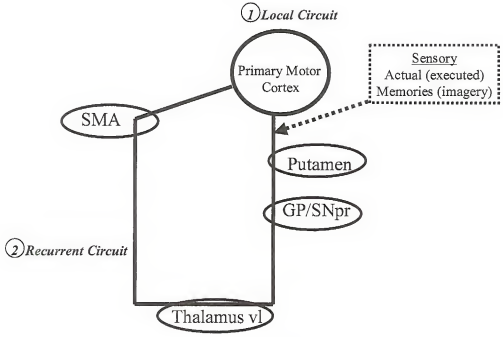


Figure 5-1. Model for closed cortico-striatial-pallido-thalmo-coritcal loop.

1) Local Circuit--Basal Ganglia loop initiates reorganization in the local circuit within the primary motor cortex. The reorganization is specific for the practiced sequence, occurs rapidly in learning process and supports accuracy of movement execution vs. speed

2) Recurrent Circuit—represents the basal ganglia loop. It supports continued improvement in performance gains. Sensory and motor cortex input shape the motor program, thus input strength is critical thus executed practice results in more robust performance changes.

As suggested, imagery may use this proposed model by substituting sensory imagery for primary motor input to the basal ganglia. Alternately the primary motor cortex may preferentially fire during imagery activating efferents to the putamen along with the imagined sensory input. In this model not enough efferents are discharged to the spinal cord to effect movement, but they are integrated into the motor loop by way of connections with the putamen. This hypothesis would be in line with studies demonstrating that imagery has been shown to selectively activate corticomotor neurons projecting to alpha-motoneurons without affecting the H-reflex [114].

Recently, Strick, Dum and Picard (1995) provide an expanded interpretation of their prior model based on recent findings that the frontal lobe contains multiple areas involved in the generation and control of limb movement including the SMA proper and pre-SMA areas [77]. Their research suggested that each cortical area preferentially projected to a topographically distinct region of the caudate and putamen. In return each cortical region appears to receive projections from topographically distinct regions within the internal segment of the globus pallidus. This arrangement leads to multiple "closed loops" and each of the six premotor areas in the frontal lobe may have its own unique loop. These findings support the proposed mechanisms described and suggest that a direct motor loop may be involved or essential to the processes described. To review, the two potential mechanisms included a closed loop that may return to SMA or pre-SMA and

secondarily synapse with primary motor cortex. Alternately, a closed loop originating and terminating at primary motor cortex may facilitate the same patterns of reorganization and motor learning seen in this study.

Subcortical Loops May Influence Primary Motor Cortex Reorganization

Both executed and imagined practice may utilize the basal ganglia as the location from which the complex motor program is developed and honed during practice sessions. Because the primary motor cortex demonstrates reorganization with learning, the original motor loop model discussed by Alexander, Delong and Strick may be expanded to include a closed loop including the primary motor cortex. The increase in cortical activation seen after practice suggests that the primary motor cortex has undergone neuroplastic change created by two factors: the local reorganization of M1 units into a network specifically representing the practiced sequence and the participation of the primary motor cortex in the cortico-striatial-pallido-thalmo-cortical loop.

While imagery produced significant improvements in motor performance, the mean increase for the group was significantly smaller than that achieved by executed motor practice. Conversely, the performance gains seen with executed movement did not uniformly translate into larger cluster volumes. One explanation may be that while imagery provides less robust stimulation of the basal ganglia, any substantial activation of the subcortical motor system leads to the development of refined motor programs. This in turn leads to increased activation of the targeted regions of the primary motor cortex that facilitate the individual sequence of movements. While the

direct performance gains may be related to the strength of the efferent signal to the basal ganglia, it may be that less robust stimulation still promotes reorganization of the primary motor cortex. A second argument, already mentioned, suggests that there is a finite change in the motor cortex that is necessary to support the practiced motor sequence and once reached, the region no longer needs to continue expansion to support the performance ie., once the additional M1 units are recruited no further adaptation in the primary motor cortex is needed . The continued improvement in performance would come from refinement of the basal ganglia motor program, not the circuitry in the primary motor cortex itself. This hypothesis would suggest that reorganization of the primary motor cortex has a time-limited role in performance gain.

The model is further supported if one considers the role of each area. The primary motor cortex has two roles, decode the motor program effecting movement and participate in the efferent limb of the motor loop. A third role may be the storage of refined motor programs; however, direct cortical stimulation often fails to elicit complex movements suggesting additional information may be necessary to access these programs if they are indeed stored locally in M1. The subcortical structures, on the other hand, have a much more demanding task. Through its association with the lateral and medial premotor cortex, parietal cortex, primary motor, and other areas, the subcortical motor system must integrate many diverse features that describe the selected movement. Each of these complex concepts are critical factors that determine how a movement is learned and ultimately repeated. It seems logical

that this process is more demanding and would take more time to develop. It may be that imagery provides a less robust stimulus to facilitate these changes. Imagery may promote reorganization of primary motor cortex, but may not be sufficient to equate with the changes produced by executed motor practice. The feedback from executed practice might be more robust than the internally generated sensations produced by imagery. If it were possible to train subjects to attend for long periods of time and create vivid imagery, the likelihood is that more robust changes in motor performance would be possible and these changes would likely coincide with increases in cortical representation as seen in robust imagers included in this study.

Random Sequence Performance and Cluster Size

Random sequences were included in the study as an internal control to determine if practice effects caused generalized increases in brain activation. It was assumed that activation of the primary motor cortex would be specific and not generalize to non-practiced sequences. This was not the case, as the random sequence demonstrated a marginally significant increase in cluster volume when the runs were averaged. Several explanations are possible. First, the changes noted in cluster size during performance of the random sequence were possibly the result of the prolonged imaging session. Random sequences were presented as the last of the three experiments. The learned sequence came before the random trials and the primary motor cortex may have been primed to perform the learned sequence once again. The activation during the random sequences was marginally significant;

however, it may be possible that the practice effect generalized recruiting the same circuits used to produce the learned sequence.

Integrating this finding into the proposed hypotheses of the interaction between the basal ganglia and the primary motor cortex, we could speculate that the random sequence was able to access the reorganized circuits of the primary motor cortex. A possible mechanism would be as follows: After three weeks of practice, the primary motor cortex undergoes reorganization that is capable of facilitating the sequenced finger motor movements. These changes are specific for the sequence practiced; however, the reorganization acts to prime the motor cortex so that tasks with similar characteristics can access the new pathways or adjacent areas of the motor cortex. This type of mechanism would allow for the rapid reorganization to support the new sequence if the "practiced" sequence was not continually reinforced. Nudo provides evidence to support this premise finding cortical motor areas regress with disuse and are overtaken by adjacent areas engaged in similar motor activity [93]. The random sequences were variations of the learned sequence and may have tapped into the reorganized circuits. Performance, specifically speed, improved on the random sequences after the three week interval; however, accuracy was decreased. The significant increase in cortical activation during the repeat of the random sequence was likely due to either a priming effect on the motor cortex or rapid adaptation to support similar movement patterns, increasing speed but not accuracy. The random sequence may not have had access to the exact neural circuitry available to the practiced sequence. It is possible that the random sequence

only utilized a portion of the reorganized circuit retaining use of adjacent cortex normally utilized to perform the random movements. The application of stereotactic head restraints and reliable test re-test conditions along with activation cluster center of mass calculations could be used to address this question more accurately. If the center of mass was not the same for the practiced and random tasks, then the concept of generalized or shared circuitry could be dismissed.

Another way of testing this hypothesis would be to conduct the current study with a placebo group who underwent the testing and scanning sessions but who did not practice any sequences at home. If this group did not show an increase in cluster size after three weeks then the finding of generalization would more likely be related to ordering effects. Regardless, the current study might have benefited from randomly arranging the order in which the tapping sequences where presented since ordering effects are known to produce false positive results in similar studies.

Correlation of Practice Effects and Changes in Cortical Activation

The final analysis that was performed compared changes in cluster size with changes in performance after the three-week practice interval. The results suggested that the only performance variable that correlated with changes in cluster size was the accuracy index. Interestingly, the correlations were only significant for the imagined and combined groups and only on the first run of the practiced sequence. The results for the executed practice group were not significant nor were any of the other analyses examining correlations involving the random sequences. The correlation between imagined practice and change in cluster size was quite robust

and stronger than the correlation between cluster size and accuracy for the combined group. Clearly, one reason for this discrepancy was that there was no relationship between cluster size and accuracy in the executed group. The executed practice group's findings were likely related to a lack of power in the current study. Visual inspection of the data suggested that several subject's performance and cluster size changes were not representative of the group as a whole. These findings suggest that a larger sample size for the executed group might demonstrate a higher correlation between changes in performance and changes in cluster size.

Of interest is the finding that only the accuracy index correlated with increases in cluster size after practice and that these changes were only significant for the first run of the practiced sequence. The use of the accuracy index favored subjects who performed the task with few errors and changes in motor cortex may code for movement accuracy more so than speed. Also the correlation was only significant for the first run of the practiced sequence. There was considerable variability in the cluster volumes over the three runs and the changes in the average were only marginally significant between the pre and post practice state. It seems the activation during the first run of the practiced sequence was the most reliable in term of correlating with the practice effect. Even though we did not find any evidence of habituation or facilitation across the runs, it remains possible that within subject trials had some interaction that limited the correlation of the average run with any of the practice variables.

Importantly, changes in cluster size for the random sequence while significant, did not correlate with any of the performance variables. This offers strong support for the idea that the increased cluster size for the practiced sequence reflects changes specific for that sequence. It seems likely that the random sequence findings were incidental and not related directly to the practice session. While the findings generalized, it seems more likely that the motor cortex was primed by the prior performance of the practiced sequence, which facilitated increased cluster sizes during random tapping. Repetition of this experiment would benefit by having the tapping sequences randomized during the scanning session to eliminate possible ordering effects. As discussed, a placebo group would also be beneficial in future studies.

In summary, when subjects reported robust imagery and imagined practice lead to performance gains, those gains were correlated with an increase in cluster volume in the post-practice state. These findings support the initial hypothesis that imagined practice can lead to changes in cortical representations. A final observation also supports this hypothesis. Subject I19 who had difficulty with imagery demonstrated not only a decrease in motor performance, but also a decrease in cluster volume after three weeks of practice. It is suggested that if robust imagery leads to improved performance and increased cluster size, then poorly performed imagery may actually degrade performance and cause regression of cortical representations for that task.

Overall Project Summary

The goals of this study were to determine if imagined practice causes primary motor cortex reorganization. Results indicated that imagined practice provided significant gains in performance and that the changes were correlated with increased activation of the primary motor cortex. Imagery produced significant improvements in performance; however, executed practice provided more robust performance gains. Interestingly, executed practice did not show a correlation with changes in cluster size, but this was likely due to a lack of power in the study. An unexpected finding was that random sequence tapping produced increases in cluster size; however, this change was not correlated with performance and likely represented a non-specific finding resulting from ordering effects.

Overall, imagined practice was shown to increase cortical representations and several hypothetical models were proposed to account for the interaction between motor learning and cortical reorganization. Future studies will be able to take advantage of new imaging techniques such as whole brain fMRI to address these questions in more detail. Most importantly, the results of this study may have implications for patient care. The ability to use imagery to improve performance is intriguing and may, in the future, lead to therapeutic interventions for patients recovering from neurologic injury or disease. The mechanisms by which imagery changes the brain are unclear; however, imagined practice has been shown to lead to behavioral manifestations including improved speed and accuracy on repeated finger

tapping sequences. Knowledge of this simple principle opens up endless opportunities for research and patient care applications.

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BIOGRAPHICAL SKETCH

Samuel Browd is a native Floridean having born and raised in Miami Florida. Following high school at Miami Killian Senior High where he became a Florida Acedemic Scholar, he attended college at the University of Florida from 1989 until 1993 where he obtaining a bachelors degree with highest honors in zoology. During his undergraduate training, Samuel was awarded the College of Liberal Arts and Sciences Undergraduate Research Achievement Award and other academic research awards from the Department of Zoology including the Zoology Honor Award for Outstanding Academic Achievement. After taking one year to do research and travel in Europe, he was accepted into the Medical Scientist Training Program at the University of Florida. During his medical school training, Samuel received multiple awards for academics and research including the Heilman Family Trust Award, American Heart Association Medical Student Research Fellowship, The Thomas Brown McClelland Trust Medical Scholarship and the Albert G. King Award for Distinguished Research. Samuel's research interests include both clinical and basic science application of functional MR imaging. Clinical research interests have included the uses of functional MR imaging and specifically its application to neurosurgical planning and intraoperative guidance. Basic research interests include understanding how cortical reorganization occurs following traumatic or congenital

brain injury and the use of imagery techniques as an adjunctive therapeutic modality for stroke patients. Samuel will pursue a career in academic neurosurgery and has been accepted to the residency program at the University of Utah to begin training in July 2000.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the College of Medicine and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May 2000

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